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(54) Title: MOLECULAR CLONES OF HIV-1 AND USES THEREOF

(57) Abstract

The present invention relates to the HIV-1 strains MN-ST1 and BA-L which are typical United States HIV-1 isotypes. The present invention relates to DNA segments encoding the envelope protein of MN-ST1 or BA-L, to DNA constructs containing such DNA segments and to host cells transformed with such contructs. The viral isolates and envelope proteins of the present invention are of value for use in vaccines and bioassays for the detection of HIV-1 infection in biological samples, such as blood bank samples.

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MOLECULAR CLONES OF HIV-1 AND USES THEREOF

BACKGROUND OF THE INVENTION

HIV-1 has been identified as the etiologic agent of the acquired immunodeficiency syndrome (AIDS) (Barre-Sinoussi et al., Science 220, 868-871, 1983; Popvic et al., Science 224, 497-500, 1984; Gallo et al., Science 224, 500-503, 1984). Infected individuals generally develop antibodies to the virus within several months of exposure (Sarngadharan et al., Science 224, 506-508, 1984), which has made possible the development of immunologically based tests which can identify most blood samples from infected individuals. This is a great advantage in diagnosis, and is vital to maintaining the maximum possible safety of samples from blood banks.

An important aspect of HIV-1 is its genetic variability (Hahn et al., Proc. Natl. Acad. Sci. U.S.A. 82, 4813-4817, 1985). This is particularly evident in the gene for the outer envelope glycoprotein (Starcich et al., Cell 45, 637-648, 1986; Alizon et al., Cell 46, 63-74, 1986; Gurgo et al., Virology 164, 531-536, 1988). Since the outer envelope glycoprotein is on the surface of the virus particle and the infected cell, it is potentially one of the primary targets of the immune system, including the target of neutralizing antibodies and cytotoxic T cells. This variability may also lead to differences in the ability of antigens from different strains of HIV-1 to be recognized by antibodies from a given individual, as well as to differences in the ability of proteins from different strains of virus to elicit an immune response which would be protective against the mixture of virus strains that exists in the at risk populations.

Several biologically active complete molecular clones of various strains of HIV-1 have been obtained and sequenced. These clones, however, seem to represent viral genotypes which are relatively atypical of United States HIV-1 isolates. In addition, several of the translational reading frames for non-structural viral proteins are not complete. Further, viruses derived from these clones do

not grow in macrophages, in contrast to many HIV-1 field isolates and, perhaps, because of this lack of ability to infect macrophages efficiently, these clones do not replicate well in chimpanzees. This latter ability is important for testing candidate vaccines in animal systems. In addition, the ability to infect macrophages is critical in evaluating the possible protective efficacy of elicited immune response since neutralization of infectivity on macrophage may differ from the better studied neutralization on T cells.

Neutralizing antibodies (Robert-Guroff et al., Nature 316, 72-74, 1985; Weiss et al., Nature 316, 69-72, 1985) have been demonstrated in infected individuals, as have cytotoxic T cells responses (Walker et al, Nature 328, 345-348, 1988). Although these do not appear to be protective, it is likely that if they were present prior to infection, they would prevent infection, especially by related strains of virus. This is supported by the finding that macaques can be protected by immunization with inactivated simian immunodeficiency virus (SIV) from infection with the homologous live virus (Murphy-Corb et al., Science 246, 1293-1297, 1989). Chimps also have been passively protected against challenge by live virus by prior administration of neutralizing antibodies to the same virus (Emini et al., J. Virol. 64, 3674-3678, 1989). One problem, however, is that at least some of the neutralizing antibodies studied depend on recognition of a variable region on the envelope (Matsushita et al., J. Virol. 62, 2107-2114, 1988; Rusche et al., Proc. Natl. Acad. Sci. U.S.A. 85, 3198-3202, 1988; Skinner et al., AIDS Res. Hum. Retroviruses 4, 187-197, 1988) called the V3 region (Starcich et al., Cell 45, 637-648, 1986).

An at least partial solution to the problem of viral heterogeneity is to identify prototypical HIV-1 strains, that is, those that are most similar by DNA sequence data or serologic reactivity to strains present in the population at risk. The inclusion of a limited number of such prototype strains in a polyvalent vaccine

cocktail might then result in elicitation of an immune response protective against most naturally occurring viruses within a given population. Such a mixture should also provide the maximum possible sensitivity in diagnostic tests for antibodies in infected individuals.

Components of highly representative isolates of a geographical area provide the maximum possible sensitivity in diagnostic tests and vaccines. Production of viral proteins from molecular clones by recombinant DNA techniques is the preferred and safest means to provide such proteins. Molecular clones of prototype HIV-1 strains can serve as the material from which such recombinant proteins can be made. The use of recombinant DNA avoids any possibility of the presence of live virus and affords the opportunity of genetically modifying viral gene products. The use of biologically active clones ensures that the gene products are functional and hence, maximizes their potential relevance.

Infectious clones, that is, those which after transfection into recipient cells produce complete virus, are desirable for several reasons. One reason is that the gene products are by definition functional; this maximizes their potential relevance to what is occurring in vivo. A second reason is that genetically altered complete virus is easy to obtain. Consequently, the biological consequences of variability can be easily assessed. For example, the effect of changes in the envelope gene on the ability of the virus to be neutralized by antibody can be easily addressed. Using this technique, a single point mutation in the envelope gene has been shown to confer resistance to neutralizing antibody (Reitz et al., Cell 54, 57-63, 1988). A third reason is that a clonal virus population provides the greatest possible definition for challenge virus in animals receiving candidate vaccines, especially those including components of the same molecularly cloned virus.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide vaccine components for an anti HIV-1 vaccine which would represent a typical United States isolate HIV-1.

It is another object of the present invention to provide diagnostic tests for the detection of HIV-1.

Various other objects and advantages of the present invention will become apparent from the drawings and the following description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the structure and restriction map of the lambda MN-PH1 clone.

FIGURE 2 shows the restriction map of the MN-PH1 envelope plasmid clone.

FIGURE 3 shows the restriction map and structure of the lambda MN-ST1 clone.

FIGURE 4 shows the structure of the lambda BA-L clone.

FIGURE 5 shows the restriction map of the clone BA-L1.

Detailed Disclosure of the Invention

The present invention relates to the HIV-1 virus strains, MN-ST1 and BA-L, which are more typical of the HIV-1 isolates found in the United States than previously known HIV-1 strains. Local isolates provide better material for vaccine and for the detection of the virus in biological samples, such as blood bank samples.

The present invention relates to DNA segments encoding the env protein of MN-ST1 or BA-L (the DNA sequence given in Figures 5 and 8 being two such examples) and to nucleotide sequences complementary to the segments referenced above as well as to other genes and nucleotide sequences contained in these clones. The present invention also relates to DNA segments encoding a unique portion of the MN-ST1 env protein or the BA-L env protein. (A "unique portion" consists of at least five (or six) amino acids or corresponding at least 15 (or 18) nucleotides.)

The invention further relates to the HIV-1 virus strains MN-ST1 and BA-L themselves. The HIV-1 virus strains of the present invention are biologically active and can easily be isolated by one skilled in the art using known methodologies.

The above-described DNA segments of the present invention can be placed in DNA constructs which are then used in the transformation of host cells for a generation of recombinantly produced viral proteins. DNA constructs of the present invention comprise a DNA segment encoding the env protein and the flanking region of MN-ST1 (or BA-L) or a portion thereof and a vector. The constructs can further comprise a second DNA segment encoding both a rev protein and a rev-responsive region of the env gene operably linked to the first DNA segment encoding the env protein. The rev protein facilitates efficient expression of the env protein in eucaryotic cells. Suitable vectors for use in the present invention include, but are not limited to, pSP72, lambda EMBL3 and SP65gpt.

Host cells to which the present invention relates are stably transformed with the above-described DNA constructs. The cells are transformed under conditions such that the viral protein encoded in the transforming construct is expressed. The host cell can be procaryotic (such as bacterial), lower eucaryotic (such as fungal, including yeast) or higher eucaryotic (such as mammalian). The host cells can be used to generate recombinantly produced MN-ST1 (or BA-L) env protein by culturing the cells in a manner allowing expression of the viral protein encoded in the construct. The recombinantly produced protein is easily isolated from the host cells using standard protein isolation protocols.

Since HIV-1 strains MN-ST1 and BA-L represent relatively typical United States genotypes, non-infectious MN-ST1 or BA-L proteins (for example, the env protein), peptides or unique portions of MN-ST1 or BA-L proteins (for example, a unique portion of the env protein), and even whole inactivated MN-ST1 or BA-L can be used as an

immunogen in mammals, such as primates, to generate antibodies capable of neutralization and T cells capable of killing infected cells. The protein can be isolated from the virus or made recombinantly from a cloned envelope gene. Accordingly, the virus and viral proteins of the present invention are of value as either a vaccine or a component thereof, or an agent in immunotherapeutic treatment of individuals already infected with HIV-1.

As is customary for vaccines, a non-infectious antigenic portion of MN-ST1 or BA-L, for example, the env protein, can be delivered to a mammal in a pharmacologically acceptable carrier. The present invention relates to vaccines comprising non-infectious antigenic portions of either MN-ST1 or BA-L and vaccines comprising non-infectious antigenic portions of both MN-ST1 and BA-L. Vaccines of the present invention can include effective amounts of immunological adjuvants known to enhance an immune response. The viral protein or polypeptide is present in the vaccine in an amount sufficient to induce an immune response against the antigenic protein and thus to protect against HIV-1 infection. Protective antibodies are usually best elicited by a series of 2-3 doses given about 2 to 3 weeks apart. The series can be repeated when circulating antibody concentration in the patient drops.

Virus derived from the infectious HIV-1(MN) clones, MN-ST1, may also be used for reproducible challenge experiments in chimpanzees treated with candidate HIV-1 vaccines or <u>in vitro</u> with human antiserum from individuals treated with candidate vaccines. A candidate vaccine can be administered to a test mammal, such as a chimpanzee prior to or simultaneously with the infectious MN-ST1 virus of the present invention. Effectiveness of the vaccine can be determined by detecting the presence or absence of HIV-1 infection in the test mammals. Side-by-side comparative tests can be run by further administering to a second set of test mammals the virus alone and comparing the number of infections which develop in the two sets of test mammals. Alternatively, candidate

vaccines can be evaluated in humans by administering the vaccine to a patient and then testing the ability of the MN-ST1 virus to infect blood cells from the patient.

The present invention also relates to the detection of HIV-1 virus in a biological sample. For detection of an HIV-1 infection, the presence of the virus, proteins encoded in the viral genome, or antibodies to HIV-1 is determined. Many types of tests, as one skilled in the art will recognize, can be used for detection. Such tests include, but are not limited to, ELISA and RIA.

In one bioassay of the present invention all, or a unique portion, of the env protein is coated on a surface and contacted with the biological sample. The presence of a resulting complex formed between the protein and antibodies specific therefor in the serum can be detected by any of the known methods commonly used in the art, such as, for example, fluorescent antibody spectroscopy or colorimetry.

The following non-limiting examples are given to further demonstrate the present invention without being deemed limitative thereof.

EXAMPLES

MN-PH1 Clone

The permuted circular unintegrated viral DNA representing the complete HIV-1(MN) genome was cloned by standard techniques (Sambrook et al., 1989, Molecular Cloning. Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press) into the Eco RI site of lambda gtWES.lambda B DNA from total DNA of H9 cells producing HIV-1(MN). This clone is designated lambda MN-PH1, and its structure and restriction map are shown in Figure 1. The clone was subcloned into M13mp18 and M13mp19, and the DNA sequence of the entire clone, given in Figure 2, was obtained by the dideoxy chain termination method (Sanger et al., Proc. Natl. Acad. Sci. U.S.A. 74, 5463-5467, 1977). The amino acid sequence of the envelope protein (see Table I) was inferred from the DNA sequence. A restriction map of the cloned unintegrated viral DNA (see

Figure 1) was also obtained from the DNA sequence of lambda PH1 and used in conjunction with the inferred amino acid sequence of the viral proteins to subclone the envelope (env) gene into the commercially available plasmid pSP72 (Promega Biological Research Products, Madison, WI), as shown in Figure 2. This plasmid (pMN-PH1env) contains, in addition to the coding regions for the envelope proteins, the coding region for the rev protein (Feinberg et al., Cell 46, 807-817, 1986) and the portion of the env gene which contains the rev-responsive region (Dayton et al., J. Acquir. Immune. Defic. Syndr. 1, 441-452, 1988), since both are necessary for efficient expression of the envelope protein in eucaryotic cells. This plasmid thus contains all the elements required for production of envelope protein following placement into appropriate expression vectors and introduction into recipient cells, all by standard techniques known to molecular biologists.

MN-ST1 Clone

The infectious molecular clone, lambda MN-ST1, was obtained by cloning integrated provirus from DNA purified from peripheral blood lymphocytes infected with HIV-1(MN) and maintained in culture for a short time (one month). The integrated proviral DNA was partially digested with the restriction enzyme Sau3A under conditions which gave a maximum yield of DNA fragments of from 15-20 kilobases (kb). This was cloned into the compatible BamHI site of lambda EMBL3, as shown in Figure 3. Figure 3 also shows the restriction map of clone lambda MN-ST1. The DNA sequence of the entire clone, given in Table II, was obtained by the dideoxy chain termination method (Sanger et al., Proc. Natl. Acad. Sci. U.S.A. 74, 5463-5467, 1977). The amino acid sequence was predicted from the DNA sequence (see Table II). This clone can be transfected into recipient cells by standard techniques. After transfection, the cloned proviral DNA is expressed into biologically active virus particles, which can be used as a source for virus stocks. The proviral DNA whose

restriction map is shown in Figure 2, was removed from the lambda phage vector by digestion with BamHI and inserted into a plasmid, SP65gpt (Feinberg et al., Cell 46, 807-817, 1986). This plasmid, pMN-ST1, contains an SV40 origin of replication. Consequently, transfection into COS-1 cells (Gluzman, Y. Cell 23, 175-182, 1981), which produce a SV40 gene product which interacts with the cognate origin of replication, results in a transient high plasmid copy number with a concomitant production of large amount of replication competent, infectious virus (Feinberg et al., Cell 46, 807-817, 1986). This provides a convenient source of genetically homogeneous virus, as well as a way to introduce desired mutations using standard methods.

The envelope gene was excised from the lambda phage clone and cloned into a plasmid as described above for lambda MN-PH1. This clone (pMN-ST1env), is similar to pMN-PH1env, described above, except that it derives from a biologically active cloned provirus. Like pMN-PH1env, it can be placed in a suitable vector and host to produce the envelope protein of HIV-1(MN) by well known techniques.

BA-L Clone

A Hind III fragment of unintegrated viral DNA representing the HIV-1(BA-L) genome was cloned by standard techniques into lambda phage Charon 28 DNA from total DNA of peripheral blood macrophages infected with and producing HIV-1(BA-L). A positive clone was selected by hybridization using a radiolabelled probe for the HIV-1 envelope. This clone, designated lambda BA-L1, was found to contain the entire gene for the envelope protein. Its structure is given in Figure 4. The insert was transferred into a plasmid (pBluescript, Stratagene, LaJolla, CA) and the DNA sequence of the env gene was determined (see Table III). This clone is designated pBA-L1.

The amino acid sequence of the envelope protein, shown in Table III, was inferred from the DNA sequence. A restriction map was also obtained from the DNA sequence of BA-L1 (shown in Figure 5) in order to determine the

appropriate restriction enzyme sites for cloning the env gene into suitable expression vectors. An Eco RI-HindIII fragment of 0.4 Kb and a 2.8 Kb HindIII-Xba1 fragment when cloned together constitute the entire env gene. This plasmid contains, in addition to the coding regions for the envelope proteins, the coding region for the rev protein and the portion of the env protein which contains the rev-responsive region. Both are necessary for efficient expression of the envelope protein in eucaryotic cells (Feinberg et al., Cell 46, 807-817, 1986; Dayton et al., J. Acquir. Immune. Defic. Syndr. 1, 441-452). This plasmid thus contains all the HIV-1 genetic elements required for production of envelope protein following placement into appropriate expression vectors and introduction into recipient cells, all by standard techniques well known in the art.

Statement of Deposit

The lambda MN-ST1 clone and the BA-L plasmid clone were deposited at the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A., on September 13, 1990, under the terms of the Budapest Treaty. The lambda MN-ST1 clone has been assigned the ATCC accession number ATCC 40889 and the BA-L plasmid clone has been assigned the ATCC accession number ATCC 40890.

* * * * * *

All publications mentioned hereinabove are hereby incorporated by reference.

While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention.

TABLE I

```
TGGAAGGGCT AATTCACTCC CAACGAAGAC AAGATATCCT TGATCTGTGG ATCTACCACA   60
CACAAGGCTA CTTCCCTGAT TAGCAGAACT ACACACCAGG GCCAGGGATC AGATATCCAC  120
TGACCTTTGG ATGGTGCTAC AAGCTAGTAC CAGTTGAGCC AGAGAAGTTA GAAGAAGCCA  180
ACAAAGGAGA GAACACCAGC TTGTTACACC CTGTGAGCCT GCATGGAATG GATGACCCGG  240
AGAGAGAAGT GTTAGAGTGG AGGTTTGACA GCCGCCTAGC ATTTCATCAC ATGGCCCGAG  300
AGCTGCATCC GGAGTACTTC AAGAACTGCT GACATCGAGC TTGCTACAAG GGACTTTCCG  360
CTGGGGACTT TCCAGGGAGG CGTGGCCTGG GCGGGACTGG GGAGTGGCGA GCCCTCAGAT  420
CCTGCATATA AGCAGCTGCT TTTTGCCTGT ACTGGGTCTC TCTGGTTAGA CCAGATCTGA  480
GCCTGGGAGC TCTCTGGCTA ACTAGGGAAC CCACTGCTTA AGCCTCAATA AAGCTTGCCT  540
TGAGTGCTTC AAGTAGTGTG TGCCCGTCTG TTATGTGACT CTGGTAGCTA GAGATCCCTC  600
AGATCCTTTT AGGCAGTGTG GAAAATCTCT AGCAGTGGCG CCCGAACAGG GACTTGAAAG  660
CGAAAGAAAA ACCAGAGCTC TCTCGACGCA GGACTCGGCT TGCTGAAGCG CGCACGGCAA  720
GAGGCGAGGG GCGGCGACTG GTGAGTACGC CAAAAATTCT TGACTAGCGG AGGCTAGAAG  780
GAGAGAGATG GGTGCGAGAG CGTCGGTATT AAGCGGGGGA GAATTAGATC GATGGGAAAA  840
CATTCGGTTA AGGCCAGGGG GAAAGAAAAA ATATAAATTA AAACATGTAG TATGGGCAAG  900
CAGGGAGCTA GAACGATTCG CAGTCAATCC TGGCCTGTTA GAAACATCAG AAGGCTGTAG  960
ACAAATACTG GGACAGCTAC AACCATCCCT TCAGACAGGA TCAGAAGAAC TTAAATCATT 1020
ATATAATACA GTAGCAACCC TCTATTGTGT GCATCAAAAG ATAGAGATAA AAGACACCAA 1080
GGAAGCTTTA GAGAAAATAG AGGAAGAGCA AAACAAAAGT AAGAAAAAAG CACAGCAAGC 1140
AGCAGCTGAC ACAGGAAACA GAGGAAACAG CAGCCAAGTC AGCCAAAATT ACCCCATAGT 1200
GCAGAACATC GAGGGGCAAA TGGTACATCA GGCCATATCA CCTAGAACTT TAAATGCATG 1260
GGTAAAAGTA GTAGAAGAGA AGGCTTTCAG CCCAGAAGTA ATACCCATGT TTTCAGCATT 1320
ATCAGAAGGA GCCACCCCAC AAGATTTAAA CACCATGCTA AACACAGTGG GGGGACATCA 1380
AGCAGCCATG CAAATGTTAA AAGAGACCAT CAATGAGGAA GCTGCAGAAT GGGATAGATT 1440
GCATCCAGTG CATGCAGGGC CTATTACACC AGGCCAGATG AGAGAACCAA GGGGAAGTGA 1500
CATAGCAGGA ACTACTAGTA CCCTTCAGGA ACAAATAGGA TGGATGACAA ATAATCCACC 1560
TATCCCAGTA GGAGAAATCT ATAAAAGATG GATAATCCTG GGATTAAATA AAATAGTAAG 1620
GATGTATAGC CCTTCCAGCA TTCTGGACAT AAGACAAGGA CCAAAGGAAC CCTTTAGAGA 1680
CTATGTAGAC CGGTTCTATA AAACTCTAAG AGCCGAGCAA GCTTCACAGG AGGTAAAAAA 1740
CCGGACGACA GAAACCTTGT TGGTCCAAAA TGCGAACCCA GATTGTAAGA CTATTTTAAA 1800
AGCATTGGGA CCAGCAGCTA CACTAGAAGA AATGATGACA GCATGTCAGG GAGTGGGAGG 1860
ACCTGGTCAT AAAGCAAGAG TTTTGGCGGA AGCGATGAGC CAAGTAACAA ATTCAGCTAC 1920
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CATAATGATG CAGAGAGGCA ATTTTAGGAA TCAAAGAAAG ATTATCAAGT GCTTCAATTG 1980

TGGCAAAGAA GGGCACATAG CCAAAAATTG CAGGGCCCCT AGGAAAAGGG GCTGTTGGAA 2040

ATGTGGAAAG GAAGGACACC AAATGAAAGA TTGTACTGAG AGACAGGCTA ATTTTTTAGG 2100

GAAGATCTGG CCTTCCTGCA AGGGAAGGCG GAATTTTCCT CAGAGCAGAA CAGAGCCAAC 2160

AGCCCCACCA GAAGAGAGCT TCAGGTTTGG GGAAGAGACA ACAACTCCCT ATCAGAAGCA 2220

GGAGAAGAAG CAGGAGACGA TAGACAAGGA CCTGTATCCT TTAGCTTCCC TCAAATCACT 2280

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GAAACTGTAC CAGTAAAATT AAAGCCAGGA ATGGATGGCC CAAAAGTTAA ACAATGGCCA 2640

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TACAATGTGC TTCCACAGGG ATGGAAAGGA TCACCAGCAA TATTCCAAAG TAGCATGACA 3060

AAAATCTTAG AGCCTTTTAG AAAACAAAAT CCAGACATAG TTATCTATCA ATACATGGAT 3120

GATTTGTATG TAGGATCTGA CTTAGAAATA GGGCAGCATA GAGCAAAAAT AGAGGAACTG 3180

AGACGACATC TGTTGAGGTG GGGATTTACC ACACCAGACA AAAAACATCA GAAAGAACCT 3240

CCATTCCTTT GGATGGGTTA TGAACTCCAT CCTGATAAAT GGACAGTACA GCCTATAGTG 3300

CTACCAGAAA AAGACAGCTG GACTGTCAAT GACATACAGA AGTTAGTGGG AAAATTGAAT 3360

TGGGCAAGTC AGATTTACGC AGGGATTAAA GTAAAGCAAT TATGTAAACT CCTTAGAGGA 3420

ACCAAAGCAC TAACAGAAGT AATACCACTA ACAGAAGAAG CAGAGCTAGA ACTGGCAGAA 3480

AACAGGGAAA TTCTAAAAGA ACCAGTACAT GGAGTGTATT ATGACCCATC AAAAGACTTA 3540

ATAGCAGAAG TACAGAAGCA GGGGCAAGGC CAATGGACAT ATCAAATTTA TCAAGAGCCA 3600

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GATGAGGATT AGAACATGGA AAAGTTTAGT AAAACACCAT ATGTATATTT CAAAGAAAGC 5160

TAAAGGACGG TTTTATAGAC ATCACTATGA AAGCACTCAT CCAAGAATAA GTTCAGAAGT 5220

ACACATCCCA CTAGGGGATG CTAGATTGGT AATAACAACA TATTGGGGTC TGCATACAGG 5280

AGAAAGAGAC TGGCATTTAG GTCAGGGAGT CTCCATAGAA TGGAGGAAAA AGAGATATAG 5340

CACACAAGTA GACCCTGACC TAGCAGACCA CCTAATTCAT CTGCATTACT TTGATTGTTT 5400

TTCAGACTCT GCCATAAGAA AGGCCATATT AGGACATAGA GTTAGTCCTA TTTGTGAATT 5460

TCAAGCAGGA CATAACAAGG TAGGACCTCT ACAGTACTTG GCACTAACAG CATTAATAAC 5520

ACCAAAAAAG ATAAAGCCAC CTTTGCCTAG TGTTAAGAAA CTGACAGAGG ATAGATGGAA 5580

CAAGCCCCAG AAGACCAAGG GCCACAGAGG GAGCCATACA ATCAATGGGC ACTAGAGCTT 5640

TTAGAGGAGC TTAAGAATGA AGCTGTTAGA CATTTTCCTA GGATATGGCT CCATGGCTTA 5700

GGGCAACATA TCTATGAAAC TTATGGGGAT ACTTGGGCAG GAGTGGAAGC CATAATAAGA 5760

ATTCTACAAC AACTGCTGTT TATTCATTTC AGAATTGGGT GTCGACATAG CAGAATAGGC 5820

ATTATTCGAC AGAGGAGAGC AAGAAATGGA GCCAGTAGAT CCTAGACTAG AGCCCTGGAA 5880

GCATCCAGGA AGTCAGCCTA AGACTGCTTG TACCACTTGC TATTGTAAAA AGTGTTGCTT 5940

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TCATTGCCAA GTTTGTTTCA CAAAAAAAGC CTTAGGCATC TCCTATGGCA GGAAGAAGCG 6000

GAGACAGCGA CGAAGAGCTC CTGAAGACAG TCAGACTCAT CAAGTTTCTC TACCAAAGCA 6060

GTAAGTAGTA CATGTAATGC AACCTTTAGT AATAGCAGCA ATAGTAGCAT TAGTAGTAGC 6120

AGGAATAATA GCAATAGTTG TGTGATCCAT AGTATTCATA GAATATAGGA AAATAAGAAG 6180

ACAAAGAAAA ATAGACAGGT TAATTGATAG AATAAGCGAA AGAGCAGAAG ACAGTGGCA  6239

ATG AGA GTG AAG GGG ATC AGG AGG AAT TAT CAG CAC TGG TGG GGA TGG    6287
Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln His Trp Trp Gly Trp
  1               5                  10                  15

GGC ACG ATG CTC CTT GGG TTA TTA ATG ATC TGT AGT GCT ACA GAA AAA    6335
Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys Ser Ala Thr Glu Lys
            20                  25                  30

TTG TGG GTC ACA GTC TAT TAT GGG GTA CCT GTG TGG AAA GAA GCA ACC    6383
Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr
        35                  40                  45

ACC ACT CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG GTA    6431
Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
    50                  55                  60

CAT AAT GTT TGG GCC ACA CAA GCC TGT GTA CCC ACA GAC CCC AAC CCA    6479
His Asn Val Trp Ala Thr Gln Ala Cys Val Pro Thr Asp Pro Asn Pro
65                  70                  75                  80

CAA GAA GTA GAA TTG GTA AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA    6527
Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp Lys
                85                  90                  95

AAT AAC ATG GTA GAA CAG ATG CAT GAG GAT ATA ATC AGT TTA TGG GAT    6575
Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
            100                 105                 110

CAA AGC CTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA    6623
Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        115                 120                 125

AAT TGC ACT GAT TTG AGG AAT ACT ACT AAT ACC AAT AAT AGT ACT GCT    6671
Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr Ala
    130                 135                 140

AAT AAC AAT AGT AAT AGC GAG GGA ACA ATA AAG GGA GGA GAA ATG AAA    6719
Asn Asn Asn Ser Asn Ser Glu Gly Thr Ile Lys Gly Gly Glu Met Lys
145                 150                 155                 160

AAC TGC TCT TTC AAT ATC ACC ACA AGC ATA AGA GAT AAG ATG CAG AAA    6767
Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Met Gln Lys
                165                 170                 175

GAA TAT GCA CTT CTT TAT AAA CTT GAT ATA GTA TCA ATA GAT AAT GAT    6815
Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Val Ser Ile Asp Asn Asp
            180                 185                 190

AGT ACC AGC TAT AGG TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA CAA    6863
Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
        195                 200                 205

GCT TGT CCA AAG ATA TCC TTT GAG CCA ATT CCC ATA CAC TAT TGT GCC    6911
Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    210                 215                 220
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CCG GCT GGT TTT GCG ATT CTA AAA TGT AAC GAT AAA AAG TTC AGT GGA   6959
Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser Gly
225                 230                 235                 240

AAA GGA TCA TGT AAA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT   7007
Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile
                245                 250                 255

AGG CCA GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA   7055
Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
            260                 265                 270

GAA GAG GTA GTA ATT AGA TCT GAG AAT TTC ACT GAT AAT GCT AAA ACC   7103
Glu Glu Val Val Ile Arg Ser Glu Asn Phe Thr Asp Asn Ala Lys Thr
        275                 280                 285

ATC ATA GTA CAT CTG AAT GAA TCT GTA CAA ATT AAT TGT ACA AGA CCC   7151
Ile Ile Val His Leu Asn Glu Ser Val Gln Ile Asn Cys Thr Arg Pro
    290                 295                 300

AAC TAC AAT AAA AGA AAA AGG ATA CAT ATA GGA CCA GGG AGA GCA TTT   7199
Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala Phe
305                 310                 315                 320

TAT ACA ACA AAA AAT ATA ATA GGA ACT ATA AGA CAA GCA CAT TGT AAC   7247
Tyr Thr Thr Lys Asn Ile Ile Gly Thr Ile Arg Gln Ala His Cys Asn
                325                 330                 335

ATT AGT AGA GCA AAA TGG AAT GAC ACT TTA AGA CAG ATA GTT AGC AAA   7295
Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser Lys
            340                 345                 350

TTA AAA GAA CAA TTT AAG AAT AAA ACA ATA GTC TTT AAT CAA TCC TCA   7343
Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Gln Ser Ser
        355                 360                 365

GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT TGT GGA GGG GAA   7391
Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
    370                 375                 380

TTT TTC TAC TGT AAT ACA TCA CCA CTG TTT AAT AGT ACT TGG AAT GGT   7439
Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Thr Trp Asn Gly
385                 390                 395                 400

AAT AAT ACT TGG AAT AAT ACT ACA GGG TCA AAT AAC AAT ATC ACA CTT   7487
Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr Leu
                405                 410                 415

CAA TGC AAA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AAA   7535
Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
            420                 425                 430

GCA ATG TAT GCC CCT CCC ATT GAA GGA CAA ATT AGA TGT TCA TCA AAT   7583
Ala Met Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser Ser Asn
        435                 440                 445

ATT ACA GGG CTA CTA TTA ACA AGA GAT GGT GGT AAG GAC ACG GAC ACG   7631
Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Lys Asp Thr Asp Thr
    450                 455                 460

AAC GAC ACC GAG ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC AAT   7679
Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
465                 470                 475                 480
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TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA ACA ATT GAA CCA TTA   7727
Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro Leu
                485                 490                 495

GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA AAA   7775
Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
            500                 505                 510

AGA GCA GCG ATA GGA GCT CTG TTC CTT GGG TTC TTA GGA GCA GCA GGA   7823
Arg Ala Ala Ile Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala Gly
        515                 520                 525

AGC ACT ATG GGC GCA GCG TCA GTG ACG CTG ACG GTA CAG GCC AGA CTA   7871
Ser Thr Met Gly Ala Ala Ser Val Thr Leu Thr Val Gln Ala Arg Leu
    530                 535                 540

TTA TTG TCT GGT ATA GTG CAA CAG CAG AAC AAT TTG CTG AGG GCC ATT   7919
Leu Leu Ser Gly Ile Val Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile
545                 550                 555                 560

GAG GCG CAA CAG CAT ATG TTG CAA CTC ACA GTC TGG GGC ATC AAG CAG   7967
Glu Ala Gln Gln His Met Leu Gln Leu Thr Val Trp Gly Ile Lys Gln
                565                 570                 575

CTC CAG GCA AGA GTC CTG GCT GTG GAA AGA TAC CTA AAG GAT CAA CAG   8015
Leu Gln Ala Arg Val Leu Ala Val Glu Arg Tyr Leu Lys Asp Gln Gln
            580                 585                 590

CTC CTG GGG TTT TGG GGT TGC TCT GGA AAA CTC ATT TGC ACC ACT ACT   8063
Leu Leu Gly Phe Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr Thr
        595                 600                 605

GTG CCT TGG AAT GCT AGT TGG AGT AAT AAA TCT CTG GAT GAT ATT TGG   8111
Val Pro Trp Asn Ala Ser Trp Ser Asn Lys Ser Leu Asp Asp Ile Trp
    610                 615                 620

AAT AAC ATG ACC TGG ATG CAG TGG GAA AGA GAA ATT GAC AAT TAC ACA   8159
Asn Asn Met Thr Trp Met Gln Trp Glu Arg Glu Ile Asp Asn Tyr Thr
625                 630                 635                 640

AGC TTA ATA TAC TCA TTA CTA GAA AAA TCG CAA ACC CAA CAA GAA AAG   8207
Ser Leu Ile Tyr Ser Leu Leu Glu Lys Ser Gln Thr Gln Gln Glu Lys
                645                 650                 655

AAT GAA CAA GAA TTA TTG GAA TTG GAT AAA TGG GCA AGT TTG TGG AAT   8255
Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn
            660                 665                 670

TGG TTT GAC ATA ACA AAT TGG CTG TGG TAT ATA AAA ATA TTC ATA ATG   8303
Trp Phe Asp Ile Thr Asn Trp Leu Trp Tyr Ile Lys Ile Phe Ile Met
        675                 680                 685

ATA GTA GGA GGC TTG GTA GGT TTA AGA ATA GTT TTT GCT GTA CTT TCT   8351
Ile Val Gly Gly Leu Val Gly Leu Arg Ile Val Phe Ala Val Leu Ser
    690                 695                 700

ATA GTG AAT AGA GTT AGG CAG GGA TAC TCA CCA TTG TCG TTG CAG ACC   8399
Ile Val Asn Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Leu Gln Thr
705                 710                 715                 720

CGC CCC CCA GTT CCG AGG GGA CCC GAC AGG CCC GAA GGA ATC GAA GAA   8447
Arg Pro Pro Val Pro Arg Gly Pro Asp Arg Pro Glu Gly Ile Glu Glu
                725                 730                 735
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GAA GGT GGA GAG AGA GAC AGA GAC ACA TCC GGT CGA TTA GTG CAT GGA   8495
Glu Gly Gly Glu Arg Asp Arg Asp Thr Ser Gly Arg Leu Val His Gly
            740                 745                 750

TTC TTA GCA ATT ATC TGG GTC GAC CTG CGG AGC CTG TTC CTC TTC AGC   8543
Phe Leu Ala Ile Ile Trp Val Asp Leu Arg Ser Leu Phe Leu Phe Ser
        755                 760                 765

TAC CAC CAC AGA GAC TTA CTC TTG ATT GCA GCG AGG ATT GTG GAA CTT   8591
Tyr His His Arg Asp Leu Leu Leu Ile Ala Ala Arg Ile Val Glu Leu
    770                 775                 780

CTG GGA CGC AGG GGG TGG GAA GTC CTC AAA TAT TGG TGG AAT CTC CTA   8639
Leu Gly Arg Arg Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn Leu Leu
785                 790                 795                 800

CAG TAT TGG AGT CAG GAA CTA AAG AGT AGT GCT GTT AGC TTG CTT AAT   8687
Gln Tyr Trp Ser Gln Glu Leu Lys Ser Ser Ala Val Ser Leu Leu Asn
                805                 810                 815

GCC ACA GCT ATA GCA GTA GCT GAG GGG ACA GAT AGG GTT ATA GAA GTA   8735
Ala Thr Ala Ile Ala Val Ala Glu Gly Thr Asp Arg Val Ile Glu Val
            820                 825                 830

CTG CAA AGA GCT GGT AGA GCT ATT CTC CAC ATA CCT ACA AGA ATA AGA   8783
Leu Gln Arg Ala Gly Arg Ala Ile Leu His Ile Pro Thr Arg Ile Arg
        835                 840                 845

CAG GGC TTG GAA AGG GCT TTG CTA TAAGATGGGT GGCAAATGGT CAAAACGTGT  8837
Gln Gly Leu Glu Arg Ala Leu Leu
    850                 855

GACTGGATGG CCTACTGTAA GGGAAAGAAT GAGACGAGCT GAACCAGCTG AGCTAGCAGC 8897

AGATGGGGTG GGAGCAGCAT CCCGAGACCT GGAAAAACAT GGAGCACTCA CAAGTAGCAA 8957

TACAGCAGCT ACCAATGCTG ATTGTGCCTG GCTAGAAGCA CAAGAGGAGG AGGAAGTGGG 9017

TTTTCCAGTC AAACCTCAGG TACCTTTAAG ACCAATGACT TACAAAGCAG CTTTAGATCT 9077

TAGCCACTTT TTAAAAGAAA AGGGGGGACT GGATGGGTTA ATTTACTCCC AAAAGAGACA 9137

AGACATCCTT GATCTGTGGG TCTACCACAC ACAAGGCTAC TTCCCTGATT GGCAGAACTA 9197

CACACCAGGG CCAGGGATCA GATATCCACT GACCTTTGGA TGGTGCTTCA AGCTAGTACC 9257

AGTTGAGCCA GAGAAGATAG AAGAGGCCAA TAAAGGAGAG AACAACTGCT TGTTACACCC 9317

TATGAGCCAG CATGGATGGA TGACCCGGAG AGAGAAGTGT TAGTGTGGAA GTCTGACAGC 9377

CACCTAGCAT TTCAGCATTA TGCCCGAGAG CTGCATCCGG AGTACTACAA GAACTGCTGA 9437

CATCGAGCTA TCTACAAGGG ACTTTCCGCT GGGGACTTTC CAGGGAGGTG TGGCCTGGGC 9497

GGGACCGGGG AGTGGCGAGC CCTCAGATCG TGCATATAAG CAGCTGCTTT CTGCCTGTAC 9557

TGGGTCTCTC TGGTTAGACC AGATCTGAGC CTGGGAGCTC TCTGGCTAAC TAGGGAACCC 9617

ACTGCTTAAG CCTCAATAAA GCTTGCCTTG AGTGCTTCAA GTAGTGTGTG CCCGTCTGTT 9677

ATGTGACTCT GGTAGCTAGA GATCCCTCAG ATCCTTTTAG GCAGTGTGGA AAATCTCTAG 9737

CA                                                                9739

Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln His Trp Trp Gly Trp
 1               5                  10                  15
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Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys Ser Ala Thr Glu Lys
                20                  25                  30

Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr
            35                  40                  45

Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        50                  55                  60

His Asn Val Trp Ala Thr Gln Ala Cys Val Pro Thr Asp Pro Asn Pro
65                  70                  75                  80

Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp Lys
                85                  90                  95

Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
            100                 105                 110

Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        115                 120                 125

Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr Ala
    130                 135                 140

Asn Asn Asn Ser Asn Ser Glu Gly Thr Ile Lys Gly Gly Glu Met Lys
145                 150                 155                 160

Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Met Gln Lys
                165                 170                 175

Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Val Ser Ile Asp Asn Asp
            180                 185                 190

Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
        195                 200                 205

Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    210                 215                 220

Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser Gly
225                 230                 235                 240

Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile
                245                 250                 255

Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
            260                 265                 270

Glu Glu Val Val Ile Arg Ser Glu Asn Phe Thr Asp Asn Ala Lys Thr
        275                 280                 285

Ile Ile Val His Leu Asn Glu Ser Val Gln Ile Asn Cys Thr Arg Pro
    290                 295                 300

Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala Phe
305                 310                 315                 320

Tyr Thr Thr Lys Asn Ile Ile Gly Thr Ile Arg Gln Ala His Cys Asn
                325                 330                 335

Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser Lys
            340                 345                 350

Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Gln Ser Ser
        355                 360                 365
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Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
370 375 380

Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Thr Trp Asn Gly
385 390 395 400

Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr Leu
405 410 415

Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
420 425 430

Ala Met Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser Ser Asn
435 440 445

Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Lys Asp Thr Asp Thr
450 455 460

Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
465 470 475 480

Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro Leu
485 490 495

Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
500 505 510

Arg Ala Ala Ile Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala Gly
515 520 525

Ser Thr Met Gly Ala Ala Ser Val Thr Leu Thr Val Gln Ala Arg Leu
530 535 540

Leu Leu Ser Gly Ile Val Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile
545 550 555 560

Glu Ala Gln Gln His Met Leu Gln Leu Thr Val Trp Gly Ile Lys Gln
565 570 575

Leu Gln Ala Arg Val Leu Ala Val Glu Arg Tyr Leu Lys Asp Gln Gln
580 585 590

Leu Leu Gly Phe Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr Thr
595 600 605

Val Pro Trp Asn Ala Ser Trp Ser Asn Lys Ser Leu Asp Asp Ile Trp
610 615 620

Asn Asn Met Thr Trp Met Gln Trp Glu Arg Glu Ile Asp Asn Tyr Thr
625 630 635 640

Ser Leu Ile Tyr Ser Leu Leu Glu Lys Ser Gln Thr Gln Gln Glu Lys
645 650 655

Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn
660 665 670

Trp Phe Asp Ile Thr Asn Trp Leu Trp Tyr Ile Lys Ile Phe Ile Met
675 680 685

Ile Val Gly Gly Leu Val Gly Leu Arg Ile Val Phe Ala Val Leu Ser
690 695 700

Ile Val Asn Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Leu Gln Thr
705 710 715 720

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Arg Pro Pro Val Pro Arg Gly Pro Asp Arg Pro Glu Gly Ile Glu Glu
                725                 730                 735

Glu Gly Gly Glu Arg Asp Arg Asp Thr Ser Gly Arg Leu Val His Gly
            740                 745                 750

Phe Leu Ala Ile Ile Trp Val Asp Leu Arg Ser Leu Phe Leu Phe Ser
        755                 760                 765

Tyr His His Arg Asp Leu Leu Leu Ile Ala Ala Arg Ile Val Glu Leu
    770                 775                 780

Leu Gly Arg Arg Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn Leu Leu
785                 790                 795                 800

Gln Tyr Trp Ser Gln Glu Leu Lys Ser Ser Ala Val Ser Leu Leu Asn
                805                 810                 815

Ala Thr Ala Ile Ala Val Ala Glu Gly Thr Asp Arg Val Ile Glu Val
            820                 825                 830

Leu Gln Arg Ala Gly Arg Ala Ile Leu His Ile Pro Thr Arg Ile Arg
        835                 840                 845

Gln Gly Leu Glu Arg Ala Leu Leu
    850                 855
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TABLE II

TGGATGGGTT AATTTACTCC CAAAGAGACA AGACATCCTT GATCTGTGGG TCTACCACAC 60

ACAAGGCTAC TTCCCTGATT GGCAGAACTA CACACCAGGG CCAGGGATCA GATATCCACT 120

GACCTTTGGA TGGTGCTTCA AGCTAGTACC AGTTGAGCCA GAGAAGATAG AAGAGGCCAA 180

TAAAGGAGAG AACAACTGCT TGTTACACCC TATGAGCCAG CATGGGATGG ATGACCCGGA 240

GAGAGAAGTG TTAGTGTGGA AGTCTGACAG CCACCTAGCA TTTCAGCATT ATGCCCGAGA 300

GCTGCATCCG GAGTACTACA AGAACTGCTG ACATCGAGCT ATCTACAAGG GACTTTCCGC 360

TGGGGACTTT CCAGGGAGGT GTGGCCTGGG CGGGACCGGG GAGTGGCGAG CCCTCAGATG 420

CTGCATATAA GCAGCTGCTT TCTGCCTGTA CTGGGTCTCT CTGGTTAGAC CAGATCTGAG 480

CCTGGGAGCT CTCTGGCTAA CTAGGGAACC CACTGCTTAA GCCTCAATAA AGCTTGCCTT 540

GAGTGCTTCA AGTAGTGTGT GCCCGTCTGT TATGTGACTC TGGTAGCTAG AGATCCCTCA 600

GATCCTTTTA GGCAGTGTGG AAAATCTCTA GCAGTGGCGC CCGAACAGGG ACTTGAAAGC 660

GAAAGAGAAA CCAGAGGAGC TCTCTCGACG CAGGACTCGG CTTGCTGAAG CGCGCACGGC 720

AAGAGGCGAG GGGCGGCGAC TGGTGAGTAC GCCAAAATTC TTGACTAGCG GAGGCTAGAA 780

GGAGAGAGAT GGGTGCGAGA GCGTCGGTAT TAAGCGGGGG AGAATTAGAT CGATGGGAAA 840

AAATTCGGTT AAGGCCAGGG GGAAAGAAAA AATATAAATT AAAACATGTA GTATGGGCAA 900

GCAGGGAGCT AGAACGATTC GCAGTCAATC CTGGCCTGTT AGAAACATCA GAAGGCTGTA 960

GACAAATACT GGGACAGCTA CAACCATCCC TTCAGACAGG ATCAGAAGAA CTTAAATCAT 1020

TATATAATAC AGTAGCAACC CTCTATTGTG TGCATCAAAA GATAGAGATA AAAGACACCA 1080

AGGAAGCTTT AGAGAAAATA GAGGAAGAGC AAAACAAAAG TAAGAAAAAA GCACAGCAAG 1140

CAGTAGCTGA CACAGGAAAC AGAGGAAACA GCAGCCAAGT CAGCCAAAAT TACCCCATAG 1200

TGCAGAACAT CCAGGGGCAA ATGGTACATC AGGCCATATC ACCTAGAACT TTAAATGCAT 1260

GGGTAAAAGT AGTAGAAGAG AAGGCTTTCA GCCCAGAAGT AATACCCATG TTTTCAGCAT 1320

TATCAGAAGG AGCCACCCCA CAAGATTTAA ACACCATGCT AAACACAGTG GGGGGACATC 1380

AAGCAGCCAT GCAAATGTTA AAAGAGACCA TCAATGAGGA AGCTGCAGAA TGGGATAGAT 1440

TGCATCCAGT GCATGCAGGG CCTATTGCAC CAGGCCAGAT GAGAGAACCA AGGGGAAGTG 1500

ACATAGCAGG AACTACTAGT ACCCTTCAGG AACAAATAGG ATGGATGACA AATAATCCAC 1560

CTATCCCAGT AGGAGAAATC TATAAAAGAT GGATAATCCT GGGATTAAAT AAAATAGTAA 1620

GGATGTATAG CCCTTCCAGC ATTCTGGACA TAAGACAAGG ACCAAAGGAA CCCTTTAGAG 1680

ACTATGTAGA CCGGTTCTAT AAAACTCTAA GAGCCGAGCA AGCTTCACAG GAGGTAAAAA 1740

ATTGGATGAC AGAAACCTTG TTGGTCCAAA ATGCGAACCC AGATTGTAAG ACTATTTTAA 1800

AAGCATTGGG ACCAGCAGCT ACACTAGAAG AAATGATGAC AGCATGTCAG GGAGTGGGAG 1860

GACCTGGTCA TAAAGCAAGA GTTTTGGCGG AAGCGATGAG CCAAGTAACA AATTCAGCTA 1920

CCATAATGAT GCAGAGAGGC AATTTTAGGA ATCAAAGAAA GATTATCAAG TGCTTCAATT 1980

GTGGCAAAGA AGGGCACATA GCCAAAAATT GCAGGGCCCC TAGGAAAAGG GGCTGTTGGA 2040

AATGTGGAAA GGAAGGACAC CAAATGAAAG ATTGTACTGA GAGACAGGCT AATTTTTTAG 2100

GGAAGATCTG GCCTTCCTGC AAGGGAAGGC AGGGAATTTT CCTCAGAGCA GAACAGAGCC 2160

AACAGCCCCA CCAGAAGAGA GCTTCAGGTT TGGGGAAGAG ACAACAACTC CCTATCAGAA 2220

GCAGGAGAAG AAGCAGGAGA CGATAGACAA GGACCTGTAT CCTTTAGCTT CCCTCAAATC 2280

ACTCTTTGGC AACGACCCAT TGTCACAATA AAGATAGGGG GGCAACTAAA GGAAGCTCTA 2340

TTAGATACAG GAGCAGATGA TACAGTATTA GAAGAAATGA ATTTGCCAGG AAGATGGAAA 2400

CCAAAAATGA TAGGGGGAAT TGGAGGTTTT ATCAAAGTAA GACAGTATGA TCAGATAACC 2460

ATAGAAATCT GTGGACATAA AGCTATAGGT ACAGTATTAG TAGGACCTAC ACCTGTCAAC 2520

ATAATTGGAA GAAATCTGTT GACTCAGCTT GGGTGCACTT TAAATTTTCC CATTAGTCCT 2580

ATTGAAACTG TACCAGTAAA ATTAAAGCCA GGAATGGATG GCCCAAAAGT TAAACAATGG 2640

CCATTGACAG AAGAAAAAAT AAAAGCATTA ATAGAAATTT GTACAGAAAT GGAAAAGGAA 2700

GGGAAAATTT CAAAAATTGG GCCTGAAAAT CCATACAATA CTCCAGTATT TGCCATAAAG 2760

AAAAAAGACA GTACTAAATG GAGAAAATTA GTAGATTTCA GAGAACTTAA TAAGAAAACT 2820

CAAGACTTCT GGGAAGTTCA ATTAGGAATA CCACATCCTG CAGGGTTAAA AAAGAAAAAA 2880

TCAGTAACAG TACTGGATGT GGGTGATGCA TATTTTTCAG TTCCCTTAGA TAAAGACTTC 2940

AGGAAGTATA CTGCATTTAC CATACCTAGT ATAAACAATG AAACACCAGG GATTAGATAT 3000

CAGTACAATG TGCTTCCACA GGGATGGAAA GGATCACCAG CAATATTCCA AAGTAGCATG 3060

ACAAAAATCT TAGAGCCTTT TAGAAAACAA AATCCAGACA TAGTTATCTA TCAATACATG 3120

GATGATTTGT ATGTAGGATC TGACTTAGAA ATAGGGCAGC ATAGAGCAAA AATAGAGGAA 3180

CTGAGACGAC ATCTGTTGAG GTGGGGATTT ACCACACCAG ACAAAAAACA TCAGAAAGAA 3240

CCTCCATTCC TTTGGATGGG TTATGAACTC CATCCTGATA AATGGACAGT ACAGCCTATA 3300

GTGCTGCCAG AAAAAGACAG CTGGACTGTC AATGACATAC AGAAGTTAGT GGGAAAATTG 3360

AATTGGGCAA GTCAAATTTA CGCAGGGATT AAAGTAAAGC AATTATGTAA ACTCCTTAGA 3420

GGAACCAAAG CACTAACAGA AGTAATACCA CTAACAGAAG AAGCAGAGCT AGAACTGGCA 3480

GAAAACAGGG AAATTCTAAA AGAACCAGTA CATGGAGTGT ATTATGACCC ATCAAAAGAC 3540

TTAATAGCAG AAGTACAGAA GCAGGGGCAA GGCCAATGGA CATATCAAAT TTATCAAGAG 3600

CCATTTAAAA ATCTGAAAAC AGGCAAATAT GCAAGAATGA GGGGTGCCCA CACTAATGAT 3660

GTAAAACAAT TAACAGAGGC AGTGCAAAAA ATAGCCACAG AAAGCATAGT AATATGGGGA 3720

AAGACTCCTA AATTTAGACT ACCCATACAA AAAGAAACAT GGGAAACATG GTGGACAGAG 3780

TATTGGCAAG CCACCTGGAT TCCTGAGTGG GAGTTTGTCA ATACCCCTCC CTTAGTGAAA 3840

TTATGGTACC AGTTAGAGAA AGAACCCATA GTAGGAGCAG AAACTTTCTA TGTAGATGGG 3900

GCAGCTAACA GGGAGACTAA AAAAGGAAAA GCAGGATATG TTACTAACAG AGGAAGACAA 3960

AAGGTTGTCT CCCTAACTGA CACAACAAAT CAGAAGACTG AGTTACAAGC AATTCATCTA 4020

GCTTTGCAAG ATTCAGGGTT AGAAGTAAAC ATAGTAACAG ACTCACAATA TGCATTAGGA 4080

ATCATTCAAG CACAACCAGA TAAAAGTGAA TCAGAGTTAG TCAGTCAAAT AATAGAGCAG 4140

TTAATAAAAA AGGAAAAGGT CTATCTGGCA TGGGTACCAG CACACAAAGG AATTGGAGGA 4200

AATGAACAAG TAGATAAATT AGTCAGTGCT GGAATCAGGA AAGTACTATT TTTAGATGGA 4260

ATAGATAAGG CCCAAGAAGA CCATGAGAAA TATCACAGTA ATTGGAGAGC AATGGCTAGT 4320

GACTTTAACC TACCACCTAT AGTAGCAAAA GAAATAGTAG CCAGCTGTGA TAAATGTCAG 4380

CTAAAAGGAG AAGCCATGCA TGGACAAGTA GACTGTAGTC CAGGAATATG GCAACTAGAT 4440

TGTACACATT TAGAAGGAAA AGTTATCCTG GTAGCAGTTC ATGTAGCCAG TGGATACATA 4500

GAAGCAGAAG TTATTCCAGC AGAGACAGGG CAGGAGACAG CATACTTTCT CTTAAAATTA 4560

GCAGGAAGAT GGCCAGTAAA AACAATACAT ACAGACAATG GCCCCAATTT CACCAGTACT 4620

ACGGTTAAGG CCGCCTGTTG GTGGGCGGGG ATCAAGCAGG AATTTGGCAT TCCCTACAAT 4680

CCCCAAAGTC AAGGAGTAAT AGAATCTATG AATAAAGAAT TAAAGAAAAT TATAGGACAG 4740

GTAAGAGATC AGGCTGAACA TCTTAAGACA GCAGTACAAA TGGCAGTATT CATCCACAAT 4800

TTTAAAAGAA AAGGGGGGAT TGGGGGGTAC AGTGCAGGGG AAAGAATAGT AGACATAATA 4860

GCAACAGACA TACAAACTAA AGAACTACAA AAACAAATTA CAAAAATTCA AAATTTTCGG 4920

GTTTATTACA GGGACAGCAG AGATCCACTT TGGAAAGGAC CAGCAAAGCT TCTCTGGAAA 4980

GGTGAAGGGG CAGTAGTAAT ACAAGATAAT AGTGACATAA AAGTAGTGCC AAGAAGAAAA 5040

GCAAAGATCA TTAGGGATTA TGGAAAACAG ATGGCAGGTG ATGATTGTGT GGCAAGTAGA 5100

CAGGATGAGG ATTAGAACAT GGAAAAGTTT AGTAAAACAC CATATGTATA TTTCAAAGAA 5160

AGCTAAAGGA TGGTTTTATA GACATCACTA TGAAAGCACT CATCCAAGAA TAAGTTCAGA 5220

AGTACACATC CCACTAGGGG ATGCTAGATT GGTAATAACA ACATATTGGG GTCTGCATAC 5280

AGGAGAAAGA GACTGGCATT TAGGTCAGGG AGTCTCCATA GAATGGAGGA AAAAGAGATA 5340

TAGCACACAA GTAGACCCTG ACCTAGCAGA CCACCTAATT CATCTGCATT ACTTTGATTG 5400

TTTTTCAGAC TCTGCCATAA GAAAGGCCAT ATTAGGACAT AGAGTTAGTC CTATTTGTGA 5460

ATTTCAAGCA GGACATAACA AGGTAGGATC TCTACAGTAC TTGGCACTAA CAGCATTAAT 5520

AACACCAAAA AAGATAAAGC CACCTTTGCC TAGTGTTAAG AAACTGACAG AGGATAGATG 5580

GAACAAGCCC CAGAAGACCA AGGGCCACAG AGGGAGCCAT ACAATCAATG GGCATTAGAG 5640

CTTTTAGAGG AGCTTAAGAA TGAAGCTGTT AGACATTTTC CTAGGATATG GCTCCATGGC 5700

TTAGGGCAAC ATATCTATGA AACTTATGGG GATACTTGGG CAGGAGTGGA AGCCATAATA 5760

AGAATTCTAC AACAACTGCT GTTTATTCAT TTCAGAATTG GGTGTCGACA TAGCAGAATA 5820

GGCATTATTC GACAGAGGAG AGCAAGAAAT GGAGCCAGTA GATCCTAGAC TAGAGCCCTG 5880

GAAGCATCCA GGAAGTCAGC CTAAGACTGC TTGTACCACT TGCTATTGTA AAAAGTGTTG 5940

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CTTTCATTGC CAAGTTTGTT TCACAAAAAA AGCCTTAGGC ATCTCCTATG GCAGGAAGAA 6000

GCGGAGACAG CGACGAAGAG CTCCTGAAGA CAGTCAGACT CATCAAGTTT CTCTACCAAA 6060

GCAGTAAGTA GTACATGTAA TGCAACCTTT AGTAATAGCA GCAATAGTAG CATTAGTAGT 6120

AGCAGGAATA ATAGCAATAG TTGTGTGATC CATAGTATTC ATAGAATATA GGAAAATAAG 6180

AAGACAAAGA AAAATAGACA GGGTAATTGA CAGAATAAGC GAAAGAGCAG AAGACAGTGG 6240

CA ATG AGA GTG AAG GGG ATC AGG AGG AAT TAT CAG CAC TGG TGG GGA      6287
   Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln His Trp Trp Gly
     1               5                  10                  15

TGG GGC ACG ATG CTC CTT GGG TTA TTA ATG ATC TGT AGT GCT ACA GAA   6335
Trp Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys Ser Ala Thr Glu
                20                  25                  30

AAA TTG TGG GTC ACA GTC TAT TAT GGG GTA CCT GTG TGG AAA GAA GCA   6383
Lys Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala
            35                  40                  45

ACC ACC ACT CTA TTT TGT GCA TCA GAT GCT AAA GCA TAT GAT ACA GAG   6431
Thr Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu
        50                  55                  60

GTA CAT AAT GTT TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC CCC AAC   6479
Val His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn
    65                  70                  75

CCA CAA GAA GTA GAA TTG GTA AAT GTG ACA GAA AAT TTT AAC ATG TGG   6527
Pro Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp
80                  85                  90                  95

AAA AAT AAC ATG GTA GAA CAG ATG CAT GAG GAT ATA ATC AGT TTA TGG   6575
Lys Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp
                100                 105                 110

GAT CAA AGC CTA AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT   6623
Asp Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr
            115                 120                 125

TTA AAT TGC ACT GAT TTG AGG AAT ACT ACT AAT ACC AAT AAT AGT ACT   6671
Leu Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr
        130                 135                 140

GCT AAT AAC AAT AGT AAT AGC GAG GGA ACA ATA AAG GGA GGA GAA ATG   6719
Ala Asn Asn Asn Ser Asn Ser Glu Gly Thr Ile Lys Gly Gly Glu Met
    145                 150                 155

AAA AAC TGC TCT TTC AAT ATC ACC ACA AGC ATA AGA GAT AAG ATG CAG   6767
Lys Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Met Gln
160                 165                 170                 175

AAA GAA TAT GCA CTT CTT TAT AAA CTT GAT ATA GTA TCA ATA AAT AAT   6815
Lys Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Val Ser Ile Asn Asn
                180                 185                 190

GAT AGT ACC AGC TAT AGG TTG ATA AGT TGT AAT ACC TCA GTC ATT ACA   6863
Asp Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr
            195                 200                 205

CAA GCT TGT CCA AAG ATA TCC TTT GAG CCA ATT CCC ATA CAC TAT TGT   6911
Gln Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys
        210                 215                 220
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GCC CCG GCT GGT TTT GCG ATT CTA AAG TGT AAC GAT AAA AAG TTC AGT   6959
Ala Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser
    225                 230                 235

GGA AAA GGA TCA TGT AAA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA   7007
Gly Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly
240                 245                 250                 255

ATT AGG CCA GTA GTA TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA   7055
Ile Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala
                260                 265                 270

GAA GAA GAG GTA GTA ATT AGA TCT GAG AAT TTC AAT GAT AAT GCT AAA   7103
Glu Glu Glu Val Val Ile Arg Ser Glu Asn Phe Asn Asp Asn Ala Lys
            275                 280                 285


ACC ATC ATA GTA CAT CTG AAT GAA TCT GTA CAA ATT AAT TGT ACA AGA   7151
Thr Ile Ile Val His Leu Asn Glu Ser Val Gln Ile Asn Cys Thr Arg
        290                 295                 300

CCC AAC TAC AAT AAA AGA AAA AGG ATA CAT ATA GGA CCA GGG AGA GCA   7199
Pro Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala
    305                 310                 315

TTT TAT ACA ACA AAA AAT ATA ATA GGA ACT ATA AGA CAA GCA CAT TGT   7247
Phe Tyr Thr Thr Lys Asn Ile Ile Gly Thr Ile Arg Gln Ala His Cys
320                 325                 330                 335

AAC ATT AGT AGA GCA AAA TGG AAT GAC ACT TTA AGA CAG ATA GTT AGC   7295
Asn Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser
                340                 345                 350

AAA TTA AAA GAA CAA TTT AAG AAT AAA ACA ATA GTC TTT AAT CAA TCC   7343
Lys Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Gln Ser
            355                 360                 365

TCA GGA GGG GAC CCA GAA ATT GTA ATG CAC AGT TTT AAT TGT GGA GGG   7391
Ser Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly
        370                 375                 380

GAA TTT TTC TAC TGT AAT ACA TCA CCA CTG TTT AAT AGT ACT TGG AAT   7439
Glu Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Thr Trp Asn
    385                 390                 395

GGT AAT AAT ACT TGG AAT AAT ACT ACA GGG TCA AAT AAC AAT ATC ACA   7487
Gly Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr
400                 405                 410                 415

CTT CAA TGC AAA ATA AAA CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA   7535
Leu Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly
                420                 425                 430


AAA GCA ATA TAT GCC CCT CCC ATT GAA GGA CAA ATT AGA TGT TCA TCA   7583
Lys Ala Ile Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser Ser
            435                 440                 445

AAT ATT ACA GGG CTA CTA TTA ACA AGA GAT GGT GGT AAG GAC ACG GAC   7631
Asn Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Lys Asp Thr Asp
        450                 455                 460

ACG AAC GAC ACC GAG ATC TTC AGA CCT GGA GGA GGA GAT ATG AGG GAC   7679
Thr Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp
    465                 470                 475
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AAT TGG AGA AGT GAA TTA TAT AAA TAT AAA GTA GTA ACA ATT GAA CCA   7727
Asn Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro
480                 485                 490                 495

TTA GGA GTA GCA CCC ACC AAG GCA AAG AGA AGA GTG GTG CAG AGA GAA   7775
Leu Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu
                500                 505                 510

AAA AGA GCA GCG ATA GGA GCT CTG TTC CTT GGG TTC TTA GGA GCA GCA   7823
Lys Arg Ala Ala Ile Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala
            515                 520                 525

GGA AGC ACT ATG GGC GCA GCG TCA GTG ACG CTG ACG GTA CAG GCC AGA   7871
Gly Ser Thr Met Gly Ala Ala Ser Val Thr Leu Thr Val Gln Ala Arg
        530                 535                 540

CTA TTA TTG TCT GGT ATA GTG CAA CAG CAG AAC AAT TTG CTG AGG GCC   7919
Leu Leu Leu Ser Gly Ile Val Gln Gln Gln Asn Asn Leu Leu Arg Ala
    545                 550                 555

ATT GAG GCG CAA CAG CAT ATG TTG CAA CTC ACA GTC TGG GGC ATC AAG   7967
Ile Glu Ala Gln Gln His Met Leu Gln Leu Thr Val Trp Gly Ile Lys
560                 565                 570                 575

CAG CTC CAG GCA AGA ATC CTG GCT GTG GAA AGA TAC CTA AAG GAT CAA   8015
Gln Leu Gln Ala Arg Ile Leu Ala Val Glu Arg Tyr Leu Lys Asp Gln
                580                 585                 590

CAG CTC CTG GGG ATT TGG GGT TGC TCT GGA AAA CTC ATT TGC ACC ACT   8063
Gln Leu Leu Gly Ile Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr
            595                 600                 605

ACT GTG CCT TGG AAT GCT AGT TGG AGT AAT AAA TCT CTG GAT GAT ATT   8111
Thr Val Pro Trp Asn Ala Ser Trp Ser Asn Lys Ser Leu Asp Asp Ile
        610                 615                 620

TGG AAT AAC ATG ACC TGG ATG CAG TGG GAA AGA GAA ATT GAC AAT TAC   8159
Trp Asn Asn Met Thr Trp Met Gln Trp Glu Arg Glu Ile Asp Asn Tyr
    625                 630                 635

ACA AGC TTA ATA TAC TCA TTA CTA GAA AAA TCG CAA ACC CAA CAA GAA   8207
Thr Ser Leu Ile Tyr Ser Leu Leu Glu Lys Ser Gln Thr Gln Gln Glu
640                 645                 650                 655

ATG AAT GAA CAA GAA TTA TTG GAA TTG GAT AAA TGG GCA AGT TTG TGG   8255
Met Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp
                660                 665                 670

AAT TGG TTT GAC ATA ACA AAT TGG CTG TGG TAT ATA AAA ATA TTC ATA   8303
Asn Trp Phe Asp Ile Thr Asn Trp Leu Trp Tyr Ile Lys Ile Phe Ile
            675                 680                 685

ATG ATA GTA GGA GGC TTG GTA GGT TTA AGA ATA GTT TTT GCT GTA CTT   8351
Met Ile Val Gly Gly Leu Val Gly Leu Arg Ile Val Phe Ala Val Leu
        690                 695                 700

TCT ATA GTG AAT AGA GTT AGG CAG GGA TAC TCA CCA TTG TCG TTG CAG   8399
Ser Ile Val Asn Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Leu Gln
    705                 710                 715

ACC CGC CCC CCA GTT CCG AGG GGA CCC GAC AGG CCC GAA GGA ATC GAA   8447
Thr Arg Pro Pro Val Pro Arg Gly Pro Asp Arg Pro Glu Gly Ile Glu
720                 725                 730                 735
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GAA GAA GGT GGA GAG AGA GAC AGA GAC ACA TCC GGT CGA TTA GTG CAT   8495
Glu Glu Gly Gly Glu Arg Asp Arg Asp Thr Ser Gly Arg Leu Val His
                740                 745                 750

GGA TTC TTA GCA ATT ATC TGG GTC GAC CTG CGG AGC CTG TTC CTC TTC   8543
Gly Phe Leu Ala Ile Ile Trp Val Asp Leu Arg Ser Leu Phe Leu Phe
            755                 760                 765

AGC TAC CAC CAC TTG AGA GAC TTA CTC TTG ATT GCA GCG AGG ATT GTG   8591
Ser Tyr His His Leu Arg Asp Leu Leu Leu Ile Ala Ala Arg Ile Val
        770                 775                 780

GAA CTT CTG GGA CGC AGG GGG TGG GAA GTC CTC AAA TAT TGG TGG AAT   8639
Glu Leu Leu Gly Arg Arg Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn
    785                 790                 795

CTC CTA CAG TAT TGG AGT CAG GAA CTA AAG AGT AGT GCT GTT AGC TTG   8687
Leu Leu Gln Tyr Trp Ser Gln Glu Leu Lys Ser Ser Ala Val Ser Leu
800                 805                 810                 815

CTT AAT GCC ACA GAT ATA GCA GTA GCT GAG GGG ACA GAT AGG GTT ATA   8735
Leu Asn Ala Thr Asp Ile Ala Val Ala Glu Gly Thr Asp Arg Val Ile
                820                 825                 830

GAA GTA CTG CAA AGA GCT GGT AGA GCT ATT CTC CAC ATA CCT ACA AGA   8783
Glu Val Leu Gln Arg Ala Gly Arg Ala Ile Leu His Ile Pro Thr Arg
            835                 840                 845

ATA AGA CAG GGC TTG GAA AGG GCT TTG CTA TAAGATGGGT GGCAAATGGT    8833
Ile Arg Gln Gly Leu Glu Arg Ala Leu Leu
        850                 855

CAAAACGTGT GACTGGATGG CCTACTGTAA GGGAAAAAAT GAGACGAGCT GAACCAGCTG 8893

AGCCAGCAGC AGATGGGGTG GGAGCAGCAT CCCGAGACCT GGAAAAACAT GGAGCACTCA 8953

CAAGTAGCAA TACAGCAGCT ACCAATGCTG ATTGTGCCTG GCTAGAAGCA CAAGAGGAGG 9013

AGGAAGTGGG TTTTCCAGTC AGACCTCAGG TACCTTTAAG ACCAATGACT TACAAAGCAG 9073

CTTTAGATCT TAGCCACTTT TTAAAAGAAA AGGGGGGACT GGATGGGTTA ATTTACTCCC 9133

AAAAGAGACA AGACATCCTT GATCTGTGGG TCTACCACAC ACAAGGCTAC TTCCCTGATT 9193

GGCAGAACTA CACACCAGGG CCAGGGATCA GATATCCACT GACCTTTGGA TGGTGCTTCA 9253

AGCTAGTACC AGTTGAGCCA GAGAAGATAG AAGAGGCCAA TAAAGGAGAG AACAACTGCT 9313

TGTTACACCC TATGAGCCAG CATGGGATGG ATGACCCGGA GAGAGAAGTG TTAGTGTGGA 9373

AGTCTGACAG CCACCTAGCA TTTCAGCATT ATGCCCGAGA GCTGCATCCG GAGTACTACA 9433

AGAACTGCTG ACATCGAGCT ATCTACAAGG GACTTTCCGC TGGGGACTTT CCAGGGAGGT 9493

GTGGCCTGGG CGGGACCGGG GAGTGGCGAG CCCTCAGATG CTGCATATAA GCAGCTGCTT 9553

TCTGCCTGTA CTGGGTCTCT CTGGTTAGAC CAGATCTGAG CCTGGGAGCT CTCTGGCTAA 9613

CTAGGGAACC CACTGCTTAA GCCTCAATAA AGCTTGCCTT GAGTGCTTCA AGTAGTGTGT 9673

GCCCGTCTGT TATGTGACTC TGGTAGCTAG AGATCCCTCA GATCCTTTTA GGCAGTGTGG 9733

AAAATCTCTA GCA                                                   9746

Met Arg Val Lys Gly Ile Arg Arg Asn Tyr Gln His Trp Trp Gly Trp
 1               5                  10                  15
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Gly Thr Met Leu Leu Gly Leu Leu Met Ile Cys Ser Ala Thr Glu Lys
                20                  25                  30

Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr
            35                  40                  45

Thr Thr Leu Phe Cys Ala Ser Asp Ala Lys Ala Tyr Asp Thr Glu Val
        50                  55                  60

His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro
65                  70                  75                  80

Gln Glu Val Glu Leu Val Asn Val Thr Glu Asn Phe Asn Met Trp Lys
                85                  90                  95

Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
            100                 105                 110

Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
        115                 120                 125

Asn Cys Thr Asp Leu Arg Asn Thr Thr Asn Thr Asn Asn Ser Thr Ala
    130                 135                 140

Asn Asn Asn Ser Asn Ser Glu Gly Thr Ile Lys Gly Gly Glu Met Lys
145                 150                 155                 160

Asn Cys Ser Phe Asn Ile Thr Thr Ser Ile Arg Asp Lys Met Gln Lys
                165                 170                 175

Glu Tyr Ala Leu Leu Tyr Lys Leu Asp Ile Val Ser Ile Asn Asn Asp
            180                 185                 190

Ser Thr Ser Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln
        195                 200                 205

Ala Cys Pro Lys Ile Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala
    210                 215                 220

Pro Ala Gly Phe Ala Ile Leu Lys Cys Asn Asp Lys Lys Phe Ser Gly
225                 230                 235                 240

Lys Gly Ser Cys Lys Asn Val Ser Thr Val Gln Cys Thr His Gly Ile
                245                 250                 255

Arg Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu
            260                 265                 270

Glu Glu Val Val Ile Arg Ser Glu Asn Phe Asn Asp Asn Ala Lys Thr
        275                 280                 285

Ile Ile Val His Leu Asn Glu Ser Val Gln Ile Asn Cys Thr Arg Pro
    290                 295                 300

Asn Tyr Asn Lys Arg Lys Arg Ile His Ile Gly Pro Gly Arg Ala Phe
305                 310                 315                 320

Tyr Thr Thr Lys Asn Ile Ile Gly Thr Ile Arg Gln Ala His Cys Asn
                325                 330                 335

Ile Ser Arg Ala Lys Trp Asn Asp Thr Leu Arg Gln Ile Val Ser Lys
            340                 345                 350

Leu Lys Glu Gln Phe Lys Asn Lys Thr Ile Val Phe Asn Gln Ser Ser
        355                 360                 365
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Gly Gly Asp Pro Glu Ile Val Met His Ser Phe Asn Cys Gly Gly Glu
    370                 375                 380

Phe Phe Tyr Cys Asn Thr Ser Pro Leu Phe Asn Ser Thr Trp Asn Gly
385                 390                 395                 400

Asn Asn Thr Trp Asn Asn Thr Thr Gly Ser Asn Asn Asn Ile Thr Leu
                405                 410                 415

Gln Cys Lys Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Lys
            420                 425                 430

Ala Ile Tyr Ala Pro Pro Ile Glu Gly Gln Ile Arg Cys Ser Ser Asn
        435                 440                 445

Ile Thr Gly Leu Leu Leu Thr Arg Asp Gly Gly Lys Asp Thr Asp Thr
    450                 455                 460

Asn Asp Thr Glu Ile Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn
465                 470                 475                 480

Trp Arg Ser Glu Leu Tyr Lys Tyr Lys Val Val Thr Ile Glu Pro Leu
                485                 490                 495

Gly Val Ala Pro Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys
            500                 505                 510

Arg Ala Ala Ile Gly Ala Leu Phe Leu Gly Phe Leu Gly Ala Ala Gly
        515                 520                 525

Ser Thr Met Gly Ala Ala Ser Val Thr Leu Thr Val Gln Ala Arg Leu
    530                 535                 540

Leu Leu Ser Gly Ile Val Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile
545                 550                 555                 560

Glu Ala Gln Gln His Met Leu Gln Leu Thr Val Trp Gly Ile Lys Gln
                565                 570                 575

Leu Gln Ala Arg Ile Leu Ala Val Glu Arg Tyr Leu Lys Asp Gln Gln
            580                 585                 590

Leu Leu Gly Ile Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr Thr
        595                 600                 605

Val Pro Trp Asn Ala Ser Trp Ser Asn Lys Ser Leu Asp Asp Ile Trp
    610                 615                 620

Asn Asn Met Thr Trp Met Gln Trp Glu Arg Glu Ile Asp Asn Tyr Thr
625                 630                 635                 640

Ser Leu Ile Tyr Ser Leu Leu Glu Lys Ser Gln Thr Gln Gln Glu Met
                645                 650                 655

Asn Glu Gln Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn
            660                 665                 670

Trp Phe Asp Ile Thr Asn Trp Leu Trp Tyr Ile Lys Ile Phe Ile Met
        675                 680                 685

Ile Val Gly Gly Leu Val Gly Leu Arg Ile Val Phe Ala Val Leu Ser
    690                 695                 700

Ile Val Asn Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Leu Gln Thr
705                 710                 715                 720
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Arg Pro Pro Val Pro Arg Gly Pro Asp Arg Pro Glu Gly Ile Glu Glu
                725                 730                 735

Glu Gly Gly Glu Arg Asp Arg Asp Thr Ser Gly Arg Leu Val His Gly
            740                 745                 750

Phe Leu Ala Ile Ile Trp Val Asp Leu Arg Ser Leu Phe Leu Phe Ser
        755                 760                 765

Tyr His His Leu Arg Asp Leu Leu Leu Ile Ala Ala Arg Ile Val Glu
    770                 775                 780

Leu Leu Gly Arg Arg Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn Leu
785                 790                 795                 800

Leu Gln Tyr Trp Ser Gln Glu Leu Lys Ser Ser Ala Val Ser Leu Leu
                805                 810                 815

Asn Ala Thr Asp Ile Ala Val Ala Glu Gly Thr Asp Arg Val Ile Glu
            820                 825                 830

Val Leu Gln Arg Ala Gly Arg Ala Ile Leu His Ile Pro Thr Arg Ile
        835                 840                 845

Arg Gln Gly Leu Glu Arg Ala Leu Leu
    850                 855
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TABLE III

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GATCAAGGGC CACAGAGGGA GCCACACAAT GAATGGACAC TAGAGCTTTT AGAGGAGCTT   60

AAGAGTGAAG CTGTTAGACA CTTTCCTAGG ATATGGCTTC ATGGCTTAGG GCAACATATC  120

TATGAAACTT ATGGGGATAC TTGGGCAGGA GTGGAAGCCA TAATAAGAAT TCTGCAACAA  180

CTGCTGTTTA TCCATTTCAG GATTGGGTGC CAACATAGCA GAATAGGTAT TATTCAACAG  240

AGGAGAGCAA GAAATGGAGC CAGTAGATCC TAAACTAGAG CCCTGGAAGC ATCCAGGAAG  300

TCAGCCTAAG ACTGCTTGTA CCACTTGCTA TTGTAAAAAG TGTTGCTTTC ATTGCCAAGT  360

TTGCTTCATA ACAAAAGGCT TAGGCATCTC CTATGGCAGG AAGAAGCGGA GACAGCGACG  420

AAGAGCTCCT CAAGACAGTG AGACTCATCA AGTTTCTCTA TCAAAGCAGT AAGTAGTACA  480

TGTAATGCAA GCTTTACAAA TATCAGCTAT AGTAGGATTA GTAGTAGCAG CAATAATAGC  540

AATAGTTGTG TGGACCATAG TATTCATAGA ATATAGGAAA ATATTAAGGC AAAGAAAAAT  600

AGACAGGTTA ATTGATAGAA TAACAGAAAG AGCAGAAGAC AGTGGCA ATG AGA GTG    656
                                                    Met Arg Val
                                                      1

ACG GAG ATC AGG AAG AGT TAT CAG CAC TGG TGG AGA TGG GGC ATC ATG     704
Thr Glu Ile Arg Lys Ser Tyr Gln His Trp Trp Arg Trp Gly Ile Met
  5                  10                  15

CTC CTT GGG ATA TTA ATG ATC TGT AAT GCT GAA GAA AAA TTG TGG GTC     752
Leu Leu Gly Ile Leu Met Ile Cys Asn Ala Glu Glu Lys Leu Trp Val
 20                  25                  30                  35

ACA GTC TAT TAT GGG GTA CCT GTG TGG AAA GAA GCA ACC ACC ACT CTA     800
Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr Thr Thr Leu
                 40                  45                  50

TTT TGT GCA TCA GAT CGT AAA GCA TAT GAT ACA GAG GTA CAT AAT GTT     848
Phe Cys Ala Ser Asp Arg Lys Ala Tyr Asp Thr Glu Val His Asn Val
            55                  60                  65

TGG GCC ACA CAT GCC TGT GTA CCC ACA GAC CCC AAC CCA CAA GAA GTA     896
Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro Gln Glu Val
        70                  75                  80

GAA TTG AAA AAT GTG ACA GAA AAT TTT AAC ATG TGG AAA AAT AAC ATG     944
Glu Leu Lys Asn Val Thr Glu Asn Phe Asn Met Trp Lys Asn Asn Met
    85                  90                  95

GTA GAA CAA ATG CAT GAG GAT ATA ATC AGT TTA TGG GAT CAA AGC CTA     992
Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp Gln Ser Leu
100                 105                 110                 115

AAG CCA TGT GTA AAA TTA ACC CCA CTC TGT GTT ACT TTA AAT TGC ACT    1040
Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu Asn Cys Thr
                120                 125                 130

GAT TTG AGG AAT GCT ACT AAT GGG AAT GAC ACT AAT ACC ACT AGT AGT    1088
Asp Leu Arg Asn Ala Thr Asn Gly Asn Asp Thr Asn Thr Thr Ser Ser
            135                 140                 145
```

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AGC AGG GGA ATG GTG GGG GGA GGA GAA ATG AAA AAT TGC TCT TTC AAT  1136
Ser Arg Gly Met Val Gly Gly Glu Met Lys Asn Cys Ser Phe Asn
        150                 155                 160

ATC ACC ACA AAC ATA AGA GGT AAG GTG CAG AAA GAA TAT GCA CTT TTT  1184
Ile Thr Thr Asn Ile Arg Gly Lys Val Gln Lys Glu Tyr Ala Leu Phe
    165                 170                 175

TAT AAA CTT GAT ATA GCA CCA ATA GAT AAT AAT AGT AAT AAT AGA TAT  1232
Tyr Lys Leu Asp Ile Ala Pro Ile Asp Asn Asn Ser Asn Asn Arg Tyr
180                 185                 190                 195

AGG TTG ATA AGT TGT AAC ACC TCA GTC ATT ACA CAG GCC TGT CCA AAG  1280
Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala Cys Pro Lys
                200                 205                 210

GTA TCC TTT GAG CCA ATT CCC ATA CAT TAT TGT GCC CCG GCT GGT TTT  1328
Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala Pro Ala Gly Phe
            215                 220                 225

GCG ATT CTA AAG TGT AAA GAT AAG AAG TTC AAT GGA AAA GGA CCA TGT  1376
Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Lys Gly Pro Cys
        230                 235                 240

ACA AAT GTC AGC ACA GTA CAA TGT ACA CAT GGA ATT AGG CCA GTA GTA  1424
Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg Pro Val Val
    245                 250                 255

TCA ACT CAA CTG CTG TTA AAT GGC AGT CTA GCA GAA GAA GAG GTA GTA  1472
Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu Glu Val Val
260                 265                 270                 275

ATT AGA TCC GCC AAT TTC GCG GAC AAT GCT AAA GTC ATA ATA GTA CAG  1520
Ile Arg Ser Ala Asn Phe Ala Asp Asn Ala Lys Val Ile Ile Val Gln
                280                 285                 290

CTG AAT GAA TCT GTA GAA ATT AAT TGT ACA AGA CCC AAC AAC AAT ACA  1568
Leu Asn Glu Ser Val Glu Ile Asn Cys Thr Arg Pro Asn Asn Asn Thr
            295                 300                 305

AGA AAA AGT ATA CAT ATA GGA CCA GGC AGA GCA TTT TAT ACA ACA GGA  1616
Arg Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr Thr Thr Gly
        310                 315                 320

GAA ATA ATA GGA GAT ATA AGA CAA GCA CAT TGT AAC CTT AGT AGA GCA  1664
Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu Ser Arg Ala
    325                 330                 335

AAA TGG AAT GAC ACT TTA AAT AAG ATA GTT ATA AAA TTA AGA GAA CAA  1712
Lys Trp Asn Asp Thr Leu Asn Lys Ile Val Ile Lys Leu Arg Glu Gln
340                 345                 350                 355

TTT GGG AAT AAA ACA ATA GTC TTT AAG CAC TCC TCA GGA GGG GAC CCA  1760
Phe Gly Asn Lys Thr Ile Val Phe Lys His Ser Ser Gly Gly Asp Pro
                360                 365                 370

GAA ATT GTG ACG CAC AGT TTT AAT TGT GGA GGG GAA TTT TTC TAC TGT  1808
Glu Ile Val Thr His Ser Phe Asn Cys Gly Gly Glu Phe Phe Tyr Cys
            375                 380                 385

AAT TCA ACA CAA CTG TTT AAT AGT ACT TGG AAT GTT ACT GAA GAG TCA  1856
Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Val Thr Glu Glu Ser
        390                 395                 400
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AAT AAC ACT GTA GAA AAT AAC ACA ATC ACA CTC CCA TGC AGA ATA AAA   1904
Asn Asn Thr Val Glu Asn Asn Thr Ile Thr Leu Pro Cys Arg Ile Lys
    405                 410                 415

CAA ATT ATA AAC ATG TGG CAG GAA GTA GGA AGA GCA ATG TAT GCC CCT   1952
Gln Ile Ile Asn Met Trp Gln Glu Val Gly Arg Ala Met Tyr Ala Pro
420                 425                 430                 435

CCC ATC AGA GGA CAA ATT AGA TGT TCA TCA AAT ATT ACA GGG CTG CTA   2000
Pro Ile Arg Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr Gly Leu Leu
                440                 445                 450

TTA ACA AGA GAT GGT GGT CCT GAG GAC AAC AAG ACC GAG GTC TTC AGA   2048
Leu Thr Arg Asp Gly Gly Pro Glu Asp Asn Lys Thr Glu Val Phe Arg
            455                 460                 465

CCT GGA GGA GGA GAT ATG AGG GAT AAT TGG AGA AGT GAA TTA TAT AAA   2096
Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu Leu Tyr Lys
        470                 475                 480

TAT AAA GTA GTA AAA ATT GAA CCA TTA GGA GTA GCA CCC ACC AAG GCA   2144
Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro Thr Lys Ala
    485                 490                 495

AAG AGA AGA GTG GTG CAG AGA GAA AAA AGA GCA GTG GGA ATA GGA GCT   2192
Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly Ile Gly Ala
500                 505                 510                 515

GTG TTC CTT GGG TTC TTG GGA GCA GCA GGA AGC ACT ATG GGC GCA GCG   2240
Val Phe Leu Gly Phe Leu Gly Ala Ala Gly Ser Thr Met Gly Ala Ala
                520                 525                 530

GCA ATG ACG CTG ACG GTA CAG GCC AGA CTA TTA TTG TCT GGT ATA GTG   2288
Ala Met Thr Leu Thr Val Gln Ala Arg Leu Leu Leu Ser Gly Ile Val
            535                 540                 545

CAA CAG CAG AAC AAT CTG CTG AGG GCT ATT GAG GCG CAA CAG CAT CTG   2336
Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln Gln His Leu
        550                 555                 560

TTG CAA CTC ACA GTC TGG GGC ATC AAG CAG CTC CAG GCA AGA GTC CTG   2384
Leu Gln Leu Thr Val Trp Gly Ile Lys Gln Leu Gln Ala Arg Val Leu
    565                 570                 575

GCT GTG GAA AGA TAC CTA AGG GAT CAA CAG CTC CTG GGG ATT TGG GGT   2432
Ala Val Glu Arg Tyr Leu Arg Asp Gln Gln Leu Leu Gly Ile Trp Gly
580                 585                 590                 595

TGC TCT GGA AAA CTC ATC TGC ACC ACT GCT GTG CCT TGG AAT GCT AGT   2480
Cys Ser Gly Lys Leu Ile Cys Thr Thr Ala Val Pro Trp Asn Ala Ser
                600                 605                 610

TGG AGT AAT AAA TCT CTG AAT AAG ATT TGG GAT AAC ATG ACC TGG ATA   2528
Trp Ser Asn Lys Ser Leu Asn Lys Ile Trp Asp Asn Met Thr Trp Ile
            615                 620                 625

GAG TGG GAC AGA GAA ATT AAC AAT TAC ACA AGC ATA ATA TAC AGC TTA   2576
Glu Trp Asp Arg Glu Ile Asn Asn Tyr Thr Ser Ile Ile Tyr Ser Leu
        630                 635                 640

ATT GAA GAA TCG CAG AAC CAA CAA GAA AAG AAT GAA CAA GAA TTA TTA   2624
Ile Glu Glu Ser Gln Asn Gln Gln Glu Lys Asn Glu Gln Glu Leu Leu
    645                 650                 655
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GAA TTA GAT AAA TGG GCA AGT TTG TGG AAT TGG TTT GAC ATA ACA AAA   2672
Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn Trp Phe Asp Ile Thr Lys
660                 665                 670                 675

TGG CTG TGG TAT ATA AAA ATA TTC ATA ATG ATA GTA GGA GGC TTG ATA   2720
Trp Leu Trp Tyr Ile Lys Ile Phe Ile Met Ile Val Gly Gly Leu Ile
                680                 685                 690

GGT TTA AGA ATA GTT TTT TCT GTA CTT TCT ATA GTG AAT AGA GTT AGG   2768
Gly Leu Arg Ile Val Phe Ser Val Leu Ser Ile Val Asn Arg Val Arg
            695                 700                 705

CAG GGA TAC TCA CCA TTA TCG TTT CAG ACC CAC CTC CCA TCC TCG AGG   2816
Gln Gly Tyr Ser Pro Leu Ser Phe Gln Thr His Leu Pro Ser Ser Arg
        710                 715                 720

GGA CCC GAC AGG CCC GGA GGA ATC GAA GAA GAA GGT GGA GAG AGA GAC   2864
Gly Pro Asp Arg Pro Gly Gly Ile Glu Glu Glu Gly Gly Glu Arg Asp
    725                 730                 735

AGA GAC AGA TCC GGT CCA TTA GTG AAC GGA TTC TTG GCG CTT ATC TGG   2912
Arg Asp Arg Ser Gly Pro Leu Val Asn Gly Phe Leu Ala Leu Ile Trp
740                 745                 750                 755

GTC GAT CTG CGG AGC CTG TTC CTC TTC AGC TAC CAC CGC TTG AGA GAC   2960
Val Asp Leu Arg Ser Leu Phe Leu Phe Ser Tyr His Arg Leu Arg Asp
                760                 765                 770

TTA CTC TTG ATT GTG ATG AGG ATT GTG GAA CTT CTG GGA CTA GCA GGG   3008
Leu Leu Leu Ile Val Met Arg Ile Val Glu Leu Leu Gly Leu Ala Gly
            775                 780                 785

GGG TGG GAA GTC CTC AAA TAT TGG TGG AAT CTC CTA CAG TAT TGG AGT   3056
Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn Leu Leu Gln Tyr Trp Ser
        790                 795                 800

CAG GAA CTA AAG AAT AGT GCT GTT AGC TTG CTC AAT GCC ACA GCT GTA   3104
Gln Glu Leu Lys Asn Ser Ala Val Ser Leu Leu Asn Ala Thr Ala Val
    805                 810                 815

GCA GTA GCT GAA GGG ACA GAT AGG GTT ATA GAA GTA TTA CAG AGA GCT   3152
Ala Val Ala Glu Gly Thr Asp Arg Val Ile Glu Val Leu Gln Arg Ala
820                 825                 830                 835

GTT AGA GCT ATT CTC CAC ATA CCT AGA AGA ATA AGA CAG GGC TTG GAA   3200
Val Arg Ala Ile Leu His Ile Pro Arg Arg Ile Arg Gln Gly Leu Glu
                840                 845                 850

AGG GCT TTG CTA TAAGATGGGT GGCAAGTGGT CAAAAAGTAG TATAGTCGTA      3252
Arg Ala Leu Leu
            855

TGGCCTGCTG TAAGGAAAAG AATGAGAAGA ACTGAGCCAG CAGCAGATGG AGTAGGAGCA 3312

GTATCTAGAG ACCTGGAAAA ACATGGAGCA ATCACAAGTA GCAATACAGC AGCTAACAAT 3372

GCTGATTGTG CCTGGCTAGA AGCACAAGAG GATGAAGAAG TGGGTTTTCC AGTCAGACCT 3432

CAGGTACCTT TAAGACCAAT GACTCGCAGT GCAGCTATAG ATCTTAGCCA CTTTTTTAAG 3492

AAAAAGGGGG GACTGGAAGG GCTAATTCAC TCCCAAAAAA GACAAGATAT CCTTGATTTG 3552

TGGGTCTACC ACACACAAGG CTACTTCCCT GATTGGCAGA ACTACACACC AGGGCCAGGG 3612

ACCAGATTTC CACTGACCTT TGGATGGTGC TTCAAGCTAG TACCAGTTGA GCCAGAGAAG 3672
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GTAGAAGAGG CCAATGAAGG AGAGAACAAC TGCTTGTCAC ACCCTATGAG CCTGCATGGG 3732

ATGGATGACC CGGAGAAAGA AGTGTTAGCA TGGAAGTTTG ACAGCAGCCT AGCATTCCAT 3792

CACGTGGCCC GAGAA 3807

Met Arg Val Thr Glu Ile Arg Lys Ser Tyr Gln His Trp Trp Arg Trp
1 5 10 15

Gly Ile Met Leu Leu Gly Ile Leu Met Ile Cys Asn Ala Glu Glu Lys
20 25 30

Leu Trp Val Thr Val Tyr Tyr Gly Val Pro Val Trp Lys Glu Ala Thr
35 40 45

Thr Thr Leu Phe Cys Ala Ser Asp Arg Lys Ala Tyr Asp Thr Glu Val
50 55 60

His Asn Val Trp Ala Thr His Ala Cys Val Pro Thr Asp Pro Asn Pro
65 70 75 80

Gln Glu Val Glu Leu Lys Asn Val Thr Glu Asn Phe Asn Met Trp Lys
85 90 95

Asn Asn Met Val Glu Gln Met His Glu Asp Ile Ile Ser Leu Trp Asp
100 105 110

Gln Ser Leu Lys Pro Cys Val Lys Leu Thr Pro Leu Cys Val Thr Leu
115 120 125

Asn Cys Thr Asp Leu Arg Asn Ala Thr Asn Gly Asn Asp Thr Asn Thr
130 135 140

Thr Ser Ser Ser Arg Gly Met Val Gly Gly Gly Glu Met Lys Asn Cys
145 150 155 160

Ser Phe Asn Ile Thr Thr Asn Ile Arg Gly Lys Val Gln Lys Glu Tyr
165 170 175

Ala Leu Phe Tyr Lys Leu Asp Ile Ala Pro Ile Asp Asn Asn Ser Asn
180 185 190

Asn Arg Tyr Arg Leu Ile Ser Cys Asn Thr Ser Val Ile Thr Gln Ala
195 200 205

Cys Pro Lys Val Ser Phe Glu Pro Ile Pro Ile His Tyr Cys Ala Pro
210 215 220

Ala Gly Phe Ala Ile Leu Lys Cys Lys Asp Lys Lys Phe Asn Gly Lys
225 230 235 240

Gly Pro Cys Thr Asn Val Ser Thr Val Gln Cys Thr His Gly Ile Arg
245 250 255

Pro Val Val Ser Thr Gln Leu Leu Leu Asn Gly Ser Leu Ala Glu Glu
260 265 270

Glu Val Val Ile Arg Ser Ala Asn Phe Ala Asp Asn Ala Lys Val Ile
275 280 285

Ile Val Gln Leu Asn Glu Ser Val Glu Ile Asn Cys Thr Arg Pro Asn
290 295 300

Asn Asn Thr Arg Lys Ser Ile His Ile Gly Pro Gly Arg Ala Phe Tyr
305 310 315 320

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Thr Thr Gly Glu Ile Ile Gly Asp Ile Arg Gln Ala His Cys Asn Leu
                325                 330                 335

Ser Arg Ala Lys Trp Asn Asp Thr Leu Asn Lys Ile Val Ile Lys Leu
            340                 345                 350

Arg Glu Gln Phe Gly Asn Lys Thr Ile Val Phe Lys His Ser Ser Gly
        355                 360                 365

Gly Asp Pro Glu Ile Val Thr His Ser Phe Asn Cys Gly Gly Glu Phe
    370                 375                 380

Phe Tyr Cys Asn Ser Thr Gln Leu Phe Asn Ser Thr Trp Asn Val Thr
385                 390                 395                 400

Glu Glu Ser Asn Asn Thr Val Glu Asn Asn Thr Ile Thr Leu Pro Cys
                405                 410                 415

Arg Ile Lys Gln Ile Ile Asn Met Trp Gln Glu Val Gly Arg Ala Met
            420                 425                 430

Tyr Ala Pro Pro Ile Arg Gly Gln Ile Arg Cys Ser Ser Asn Ile Thr
        435                 440                 445

Gly Leu Leu Leu Thr Arg Asp Gly Gly Pro Glu Asp Asn Lys Thr Glu
    450                 455                 460

Val Phe Arg Pro Gly Gly Gly Asp Met Arg Asp Asn Trp Arg Ser Glu
465                 470                 475                 480

Leu Tyr Lys Tyr Lys Val Val Lys Ile Glu Pro Leu Gly Val Ala Pro
                485                 490                 495

Thr Lys Ala Lys Arg Arg Val Val Gln Arg Glu Lys Arg Ala Val Gly
            500                 505                 510

Ile Gly Ala Val Phe Leu Gly Phe Leu Gly Ala Ala Gly Ser Thr Met
        515                 520                 525

Gly Ala Ala Ala Met Thr Leu Thr Val Gln Ala Arg Leu Leu Leu Ser
    530                 535                 540

Gly Ile Val Gln Gln Gln Asn Asn Leu Leu Arg Ala Ile Glu Ala Gln
545                 550                 555                 560

Gln His Leu Leu Gln Leu Thr Val Trp Gly Ile Lys Gln Leu Gln Ala
                565                 570                 575

Arg Val Leu Ala Val Glu Arg Tyr Leu Arg Asp Gln Gln Leu Leu Gly
            580                 585                 590

Ile Trp Gly Cys Ser Gly Lys Leu Ile Cys Thr Thr Ala Val Pro Trp
        595                 600                 605

Asn Ala Ser Trp Ser Asn Lys Ser Leu Asn Lys Ile Trp Asp Asn Met
    610                 615                 620

Thr Trp Ile Glu Trp Asp Arg Glu Ile Asn Asn Tyr Thr Ser Ile Ile
625                 630                 635                 640

Tyr Ser Leu Ile Glu Glu Ser Gln Asn Gln Gln Glu Lys Asn Glu Gln
                645                 650                 655

Glu Leu Leu Glu Leu Asp Lys Trp Ala Ser Leu Trp Asn Trp Phe Asp
            660                 665                 670
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Ile Thr Lys Trp Leu Trp Tyr Ile Lys Ile Phe Ile Met Ile Val Gly
        675                 680                 685

Gly Leu Ile Gly Leu Arg Ile Val Phe Ser Val Leu Ser Ile Val Asn
    690                 695                 700

Arg Val Arg Gln Gly Tyr Ser Pro Leu Ser Phe Gln Thr His Leu Pro
705                 710                 715                 720

Ser Ser Arg Gly Pro Asp Arg Pro Gly Gly Ile Glu Glu Glu Gly Gly
                725                 730                 735

Glu Arg Asp Arg Asp Arg Ser Gly Pro Leu Val Asn Gly Phe Leu Ala
            740                 745                 750

Leu Ile Trp Val Asp Leu Arg Ser Leu Phe Leu Phe Ser Tyr His Arg
        755                 760                 765

Leu Arg Asp Leu Leu Leu Ile Val Met Arg Ile Val Glu Leu Leu Gly
    770                 775                 780

Leu Ala Gly Gly Trp Glu Val Leu Lys Tyr Trp Trp Asn Leu Leu Gln
785                 790                 795                 800

Tyr Trp Ser Gln Glu Leu Lys Asn Ser Ala Val Ser Leu Leu Asn Ala
                805                 810                 815

Thr Ala Val Ala Val Ala Glu Gly Thr Asp Arg Val Ile Glu Val Leu
            820                 825                 830

Gln Arg Ala Val Arg Ala Ile Leu His Ile Pro Arg Arg Ile Arg Gln
        835                 840                 845

Gly Leu Glu Arg Ala Leu Leu
    850                 855
```

WHAT IS CLAIMED IS:

1. A substantially pure preparation of a molecular clone capable of yielding after transfection into recipient cells active cultures of the Human Immunodeficiency Virus Type 1 (HIV-1) virus strain MN-ST1, having the identifying characteristics of ATCC 40889.

2. A substantially pure preparation of DNA containing the envelope and rev coding sequences of the (HIV-1) virus strain BA-L, having the identifying characteristics of ATCC 40890.

3. A DNA segment encoding an envelope (env) protein of MN-ST1.

4. The DNA segment according to claim 3 having the sequence given in Table III.

5. A DNA segment encoding an env protein of BA-L.

6. A DNA segment according to claim 5 having the sequence given in Table III.

7. A purified MN-ST1 env protein.

8. The protein according to claim 7 having the sequence given in Table II.

9. A purified BA-L protein.

10. The protein according to claim 9 having the sequence given in Table III.

11. A DNA construct comprising:

i) the DNA segment according to claim 3; and

ii) a vector.

12. The DNA construct according to claim 11 further comprising a DNA segment encoding a rev protein and a rev-responsive region.

13. A DNA construct comprising:

i) the DNA segment according to claim 5; and

ii) a vector.

14. The DNA construct according to claim 13 further comprising a DNA segment encoding a rev protein and a rev-responsive region.

15. A recombinantly produced MN-ST1 env protein.

16. A recombinantly produced BA-L env protein.

17. A host cell stably transformed with said recombinant DNA construct according to claim 11 or claim 13, in a manner allowing expression of said viral protein encoded in said recombinant DNA molecule.

18. A method of producing a recombinant HIV-1 virus strain MN-ST1 protein comprising culturing said host cells according to claim 17, in a manner allowing expression of said viral protein and isolating said viral protein.

19. A vaccine for mammals against HIV-1 infection comprising a non-infectious antigenic portion of said MN-ST1 virus strain according to claim 1, in an amount sufficient to induce immunization against said infection, and a pharmaceutically acceptable carrier.

20. A vaccine for mammals against HIV-infection comprising a non-infectious antigenic portion of said BA-L virus strain according to claim 2 in an amount sufficient to induce immunization against said infection, and a pharmaceutically acceptable carrier.

21. The vaccine according to claim 19 or claim 20 which further comprises an adjuvant.

22. A vaccine for mammals against HIV-1 infection comprising at least 5 amino acids of a MN-ST1 virus strain env protein, in an amount sufficient to induce immunization against said infection, and a pharmaceutically acceptable carrier.

23. A vaccine for mammals against HIV-1 infection comprising at least 5 amino acids of a BA-L virus strain env protein, in an amount sufficient to induce immunization against said infection, and a pharmaceutically acceptable carrier.

24. The vaccine according to claim 22 or 23 wherein said protein is a recombinantly produced protein.

25. A method of testing candidate vaccines against HIV-1 infection comprising administering said vaccine and the MN-ST1 virus strain according to claim 1,

to a test mammal and detecting the presence or absence of said infection.

26. A method of screening drugs for their ability to effect HIV-1 activity comprising contacting host cells according to claim 17, with said drug under conditions such that said activity of said virus can be effected.

27. A bioassay for the detection of HIV-1 in a biological sample comprising the steps of:

i) coating a surface with at least 5 amino acids of a env protein from MN-ST1 or BA-L virus;

ii) contacting said coated surface with said sample; and

iii) detecting the presence or absence of a complex formed between said protein and antibodies specific therefor present in said sample.

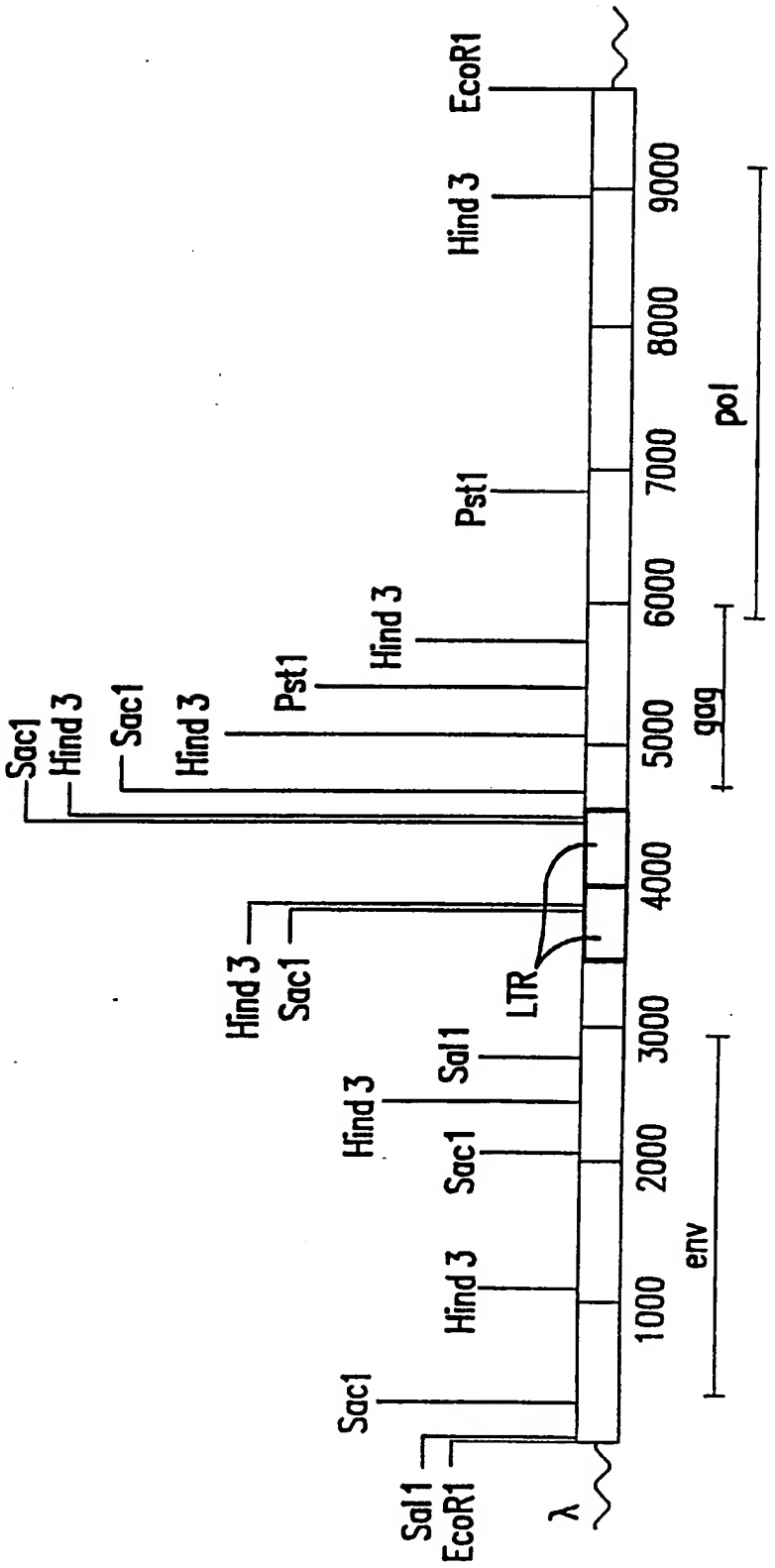

Sal1
EcoR1
λ
Sac1
Hind 3
Sac1
Hind 3
Sal1
Hind 3
Sac1
LTR
Hind 3
Sac1
Pst1
Hind 3
Sac1
Hind 3
Pst1
EcoR1
1000
2000
3000
4000
5000
6000
7000
8000
9000
env
gag
pol

FIG. 1

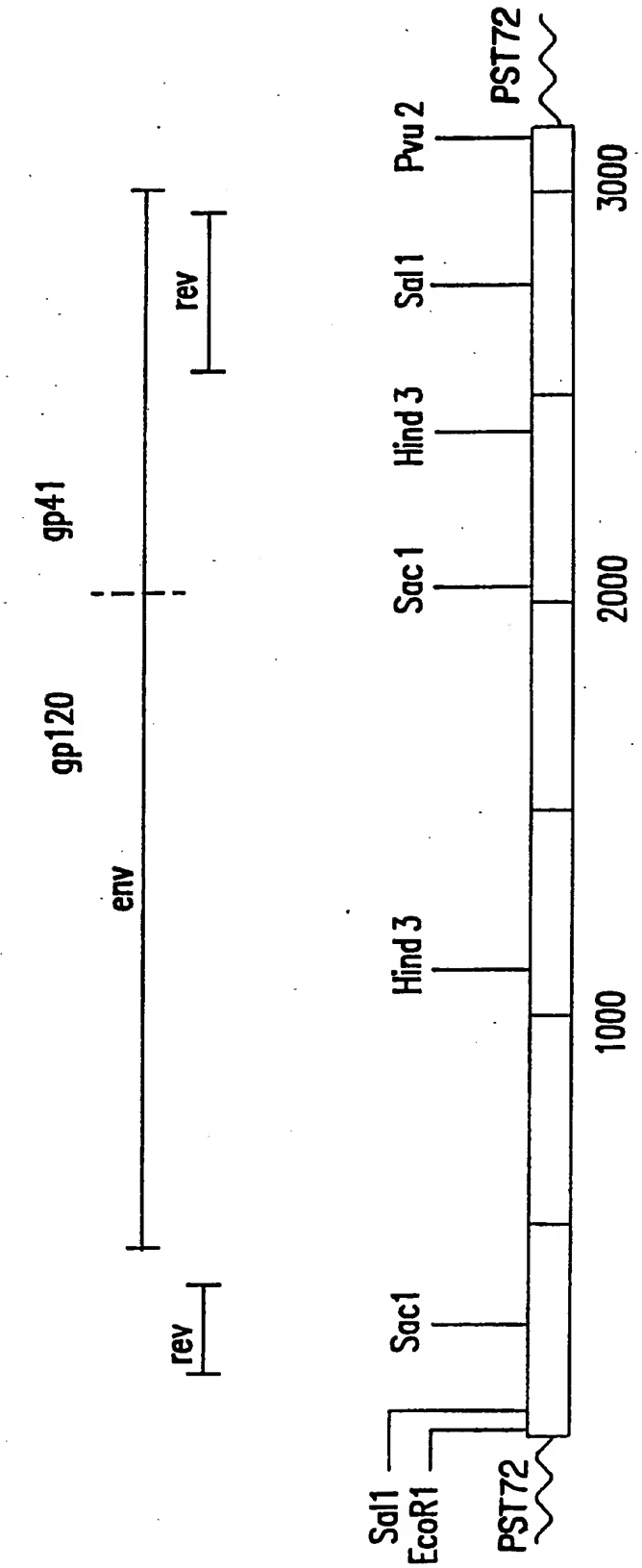
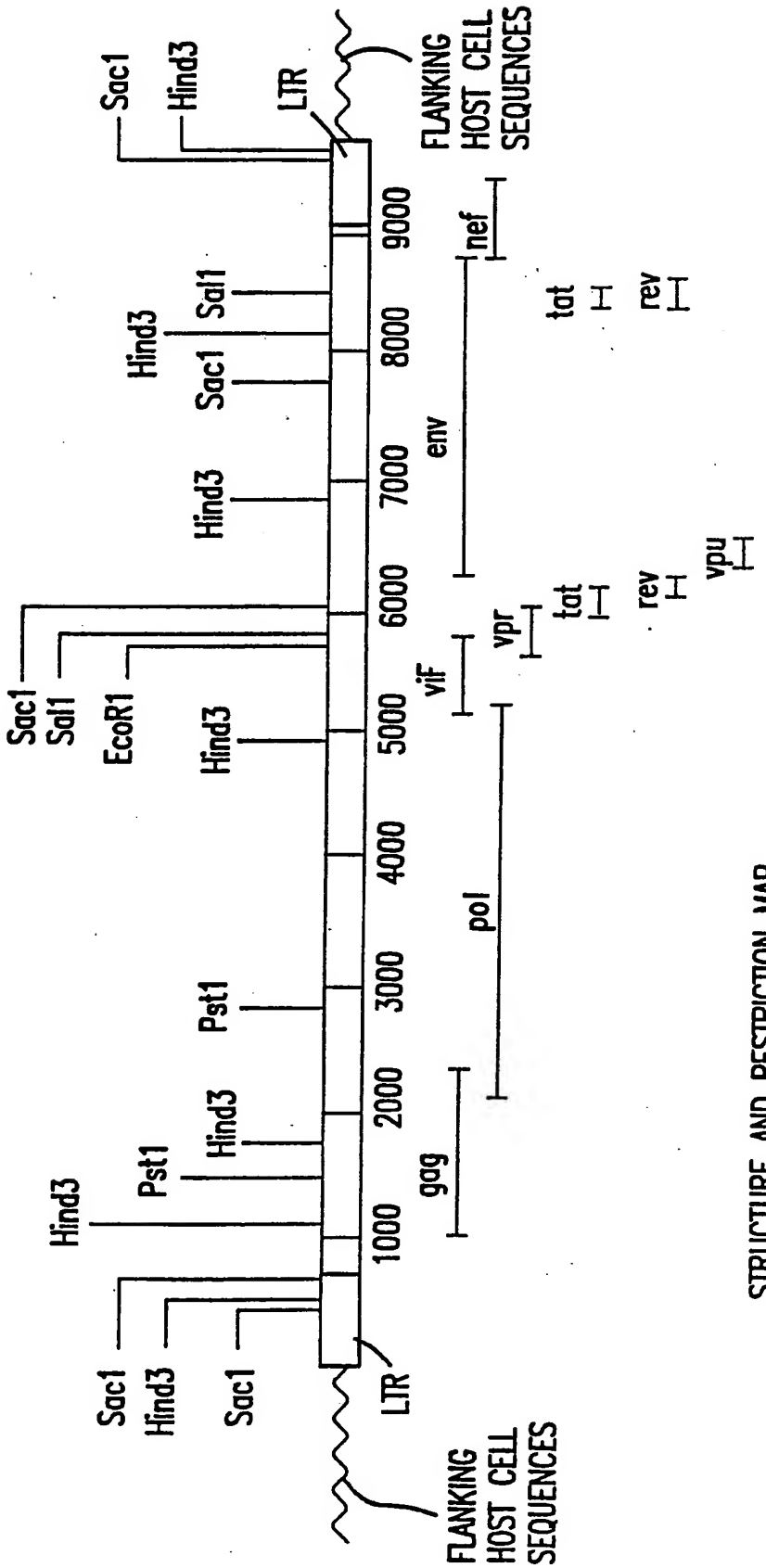

PST72
Pvu 2
Sal 1
Hind 3
Sac 1
Hind 3
Sac1
Sal1
EcoR1
PST72
3000
2000
1000
gp41
gp120
env
rev
rev
RESTRICTION MAP OF pMN-PH1 (env)

FIG. 2



STRUCTURE AND RESTRICTION MAP OF LAMBDA MN-ST1

FIG.3

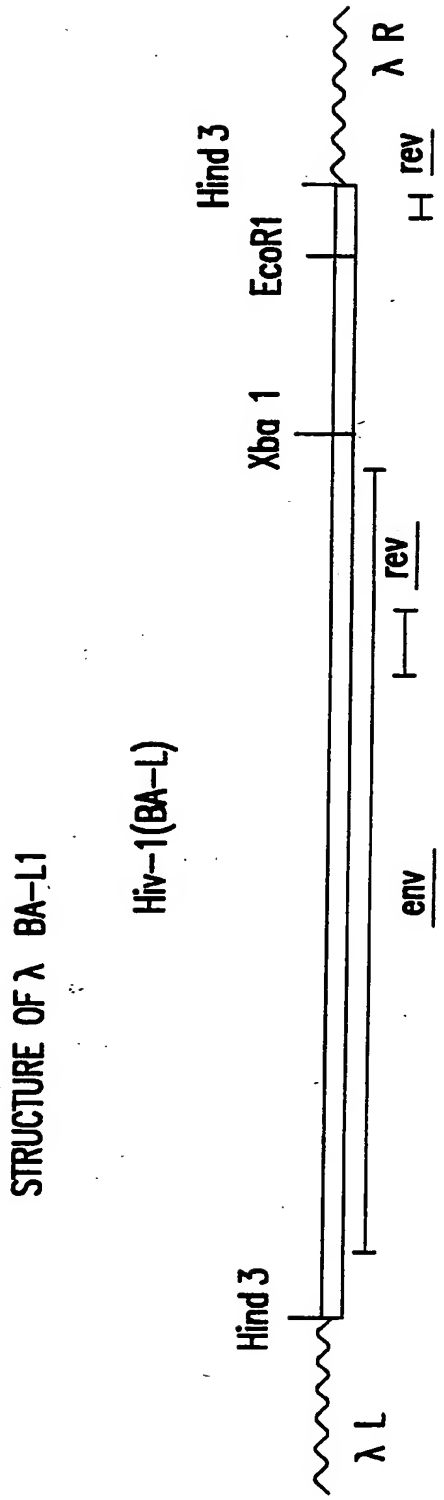

STRUCTURE OF λ BA-L1
Hiv-1(BA-L)
Hind 3
Xba 1
EcoR1
Hind 3
λ L
λ R
env
rev
rev

FIG.4

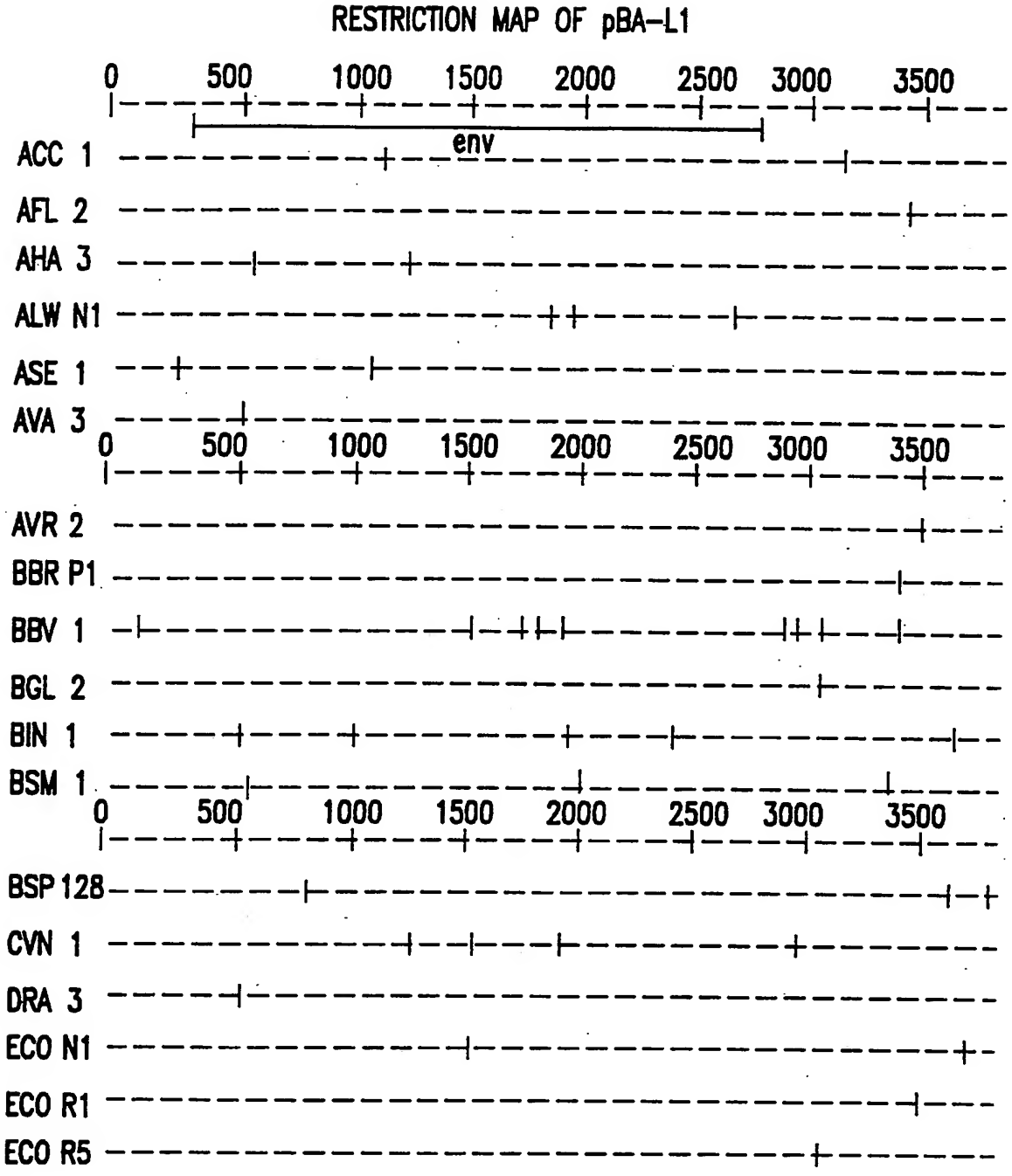

RESTRICTION MAP OF pBA-L1
0
500
1000
1500
2000
2500
3000
3500
env
ACC 1
AFL 2
AHA 3
ALW N1
ASE 1
AVA 3
AVR 2
BBR P1
BBV 1
BGL 2
BIN 1
BSM 1
BSP 128
CVN 1
DRA 3
ECO N1
ECO R1
ECO R5

FIG.5A

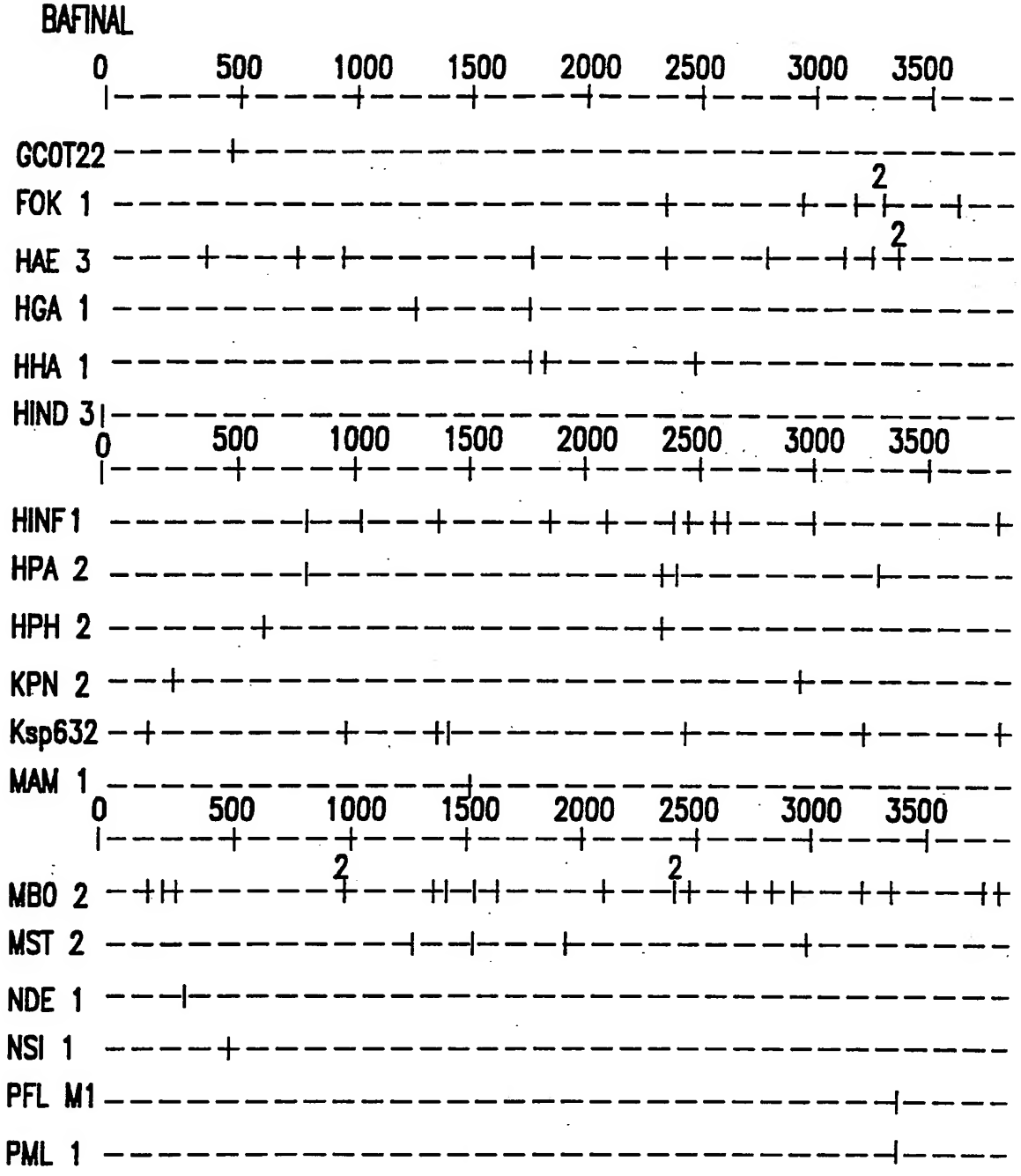

BAFINAL
0 500 1000 1500 2000 2500 3000 3500
GCOT22
FOK 1
HAE 3
HGA 1
HHA 1
HIND 3
0 500 1000 1500 2000 2500 3000 3500
HINF1
HPA 2
HPH 2
KPN 2
Ksp632
MAM 1
0 500 1000 1500 2000 2500 3000 3500
MBO 2
MST 2
NDE 1
NSI 1
PFL M1
PML 1

FIG.5B

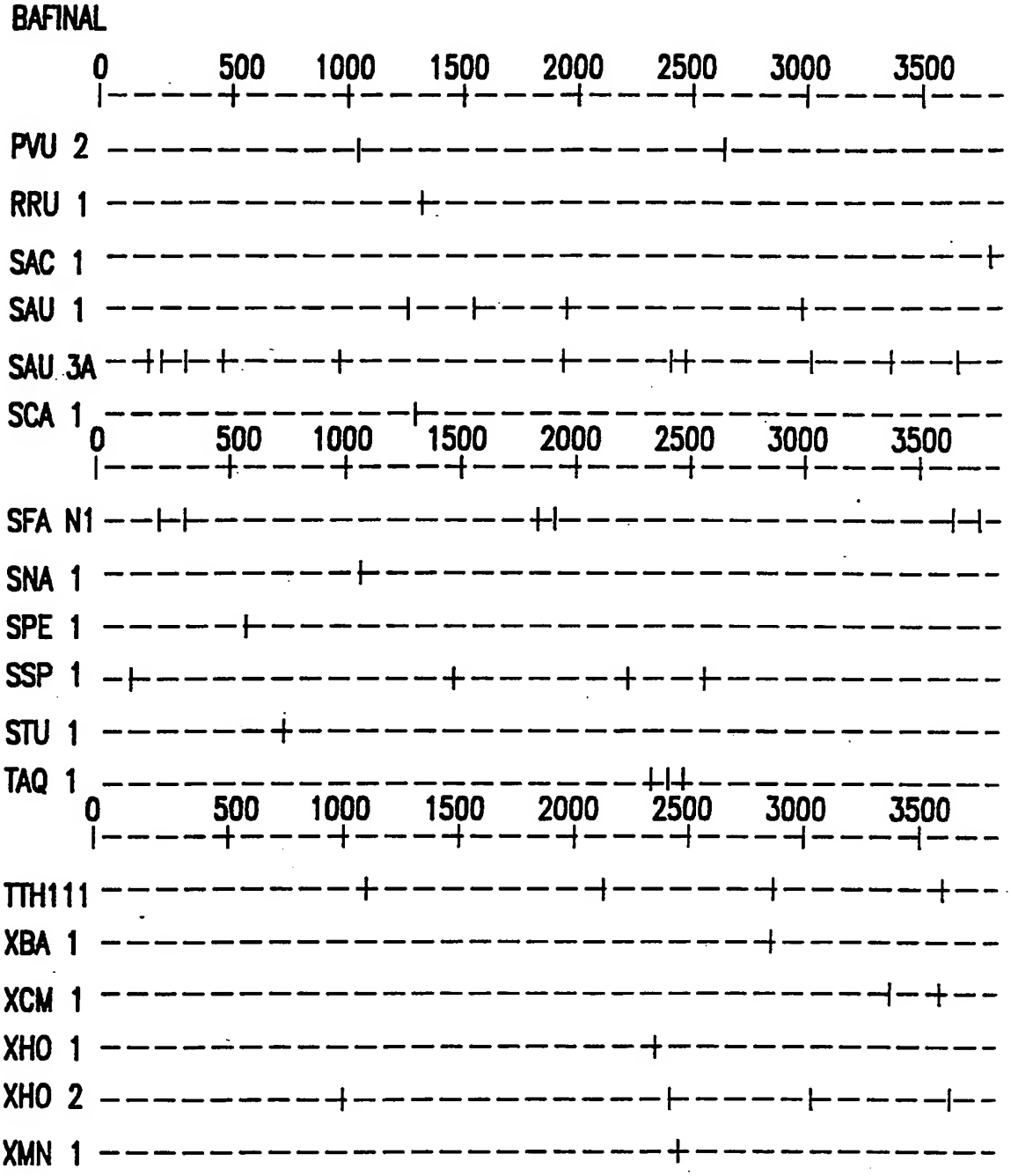

BAFINAL
0 500 1000 1500 2000 2500 3000 3500
PVU 2
RRU 1
SAC 1
SAU 1
SAU 3A
SCA 1
0 500 1000 1500 2000 2500 3000 3500
SFA N1
SNA 1
SPE 1
SSP 1
STU 1
TAQ 1
0 500 1000 1500 2000 2500 3000 3500
TTH111
XBA 1
XCM 1
XHO 1
XHO 2
XMN 1

FIG.5C

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/07611

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07H 15/12; C12N 5/10, 7/02, 7/04, 15/49; C07K 3/12, 13/00, 17/00; C12Q 1/70; A61K 39/10; G01N 33/53

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	435/7.1, 235.1, 236, 240.1; 530/350; 536/27; 424/88

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

DIALOG DATABASES: BIOSIS PREVIEWS 1985+, MEDLINE 1975+, NTIS, AIDSLINE, CA SEARCH, BIOTECHNOLOGY ABSTRACTS 1982+

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
Y	Science, Vol. 241, issued 22 July 1988, W. C. Koff et al, "Development and Testing of AIDS Vaccines," pages 426-432. See entire article.	1-24, 27
Y	Nature, Vol. 312, issued 20/27 December 1984, P. A. Luciw et al, "Molecular cloning of AIDS-associated retrovirus," pages 760-763. See entire article.	1-24, 27
Y	Science, Vol. 226, issued 07 December 1984, G. M. Shaw et al, "Molecular Characterization of Human T-Cell Leukemia (Lymphotropic) Virus Type III in the Acquired Immune Deficiency Syndrome," pages 1165-1171. See entire document.	1-24, 27
Y	Nature, Vol. 312, issued 20/27 December 1984, M. Alizon et al, "Molecular cloning of lymphadenopathy-associated virus," pages 757-760. See entire article.	1-24, 27

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

15 JANUARY 1991

Date of Mailing of this International Search Report

30 JAN 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

Johnny F. Railey II

JOHNNY F. RAILEY II

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

Y	Journal of Medical Virology, Vol. 19, issued 1986, H. Rübsamen-Waigmann et al, "Isolation of Variants of Lymphocytopathic Retroviruses From the Peripheral Blood and Cerebrospinal Fluid of Patients With ARC or AIDS," pages 335-344. See entire article.	1-24, 27
Y	Nature, Vol. 313, issued 24 January 1985, L. Ratner et al, "Complete nucleotide sequence of the AIDS virus, HTLV-III," pages 277-284. See entire article.	1-24, 27

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons

1 [ ] Claim numbers . because they relate to subject matter [1] not required to be searched by this Authority, namely:

2 [X] Claim numbers 25, 26 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [1], specifically:

Claims 25 and 26 are so vague and indefinite as to prevent a meaningful and thorough search.

3. [ ] Claim numbers_____, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [X] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

See attachment

1. [X] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4 [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[X] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Attachment to Form PCT/ISA/210, Part VI
Continuation of OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group I: Claims 1 and 25, drawn to a first product, cloned HIV-1 strain MN-ST1, and the first appearing use of the product, a method of testing vaccines against HIV-1 using strain MN-ST1.

Group II: Claims 2, 5, 6, 13 and 14, drawn to a second product, HIV-1 strain BA-L env and rev coding sequences, DNA segments encoding the env gene, and vector constructs containing these sequences.

Group III: Claims 3, 4, 11 and 12, drawn to a third product, DNA encoding strain MN-ST1 env gene and vectors containing this env gene.

Group IV: Claim 17 (first species), drawn to a fourth product, host cells stably transformed with recombinant construct of claim 11.

Group V: Claim 17 (second species), drawn to a fifth product, host cells stably transformed with recombinant construct of claim 13.

Group VI: Claim 18 (first species), drawn to a method of use of the fourth product, host cells transformed with the recombinant construct of claim 11.

Group VII: Claim 18 (second species), drawn to a method of use of the fifth product, host cells transformed with the recombinant construct of claim 13.

Group VIII: Claims 7, 8 and 15, drawn to a sixth product, HIV-1 strain MN-ST1 env protein.

Group IX: Claims 9, 10 and 16, drawn to a seventh product, HIV-1 strain BA-L env protein.

Group X: Claims 19 and 21 (first species), drawn to an eighth product, vaccines using MN-ST1.

Group XI: Claims 20 and 21 (second species), drawn to a ninth product, vaccines using BA-L.

Attachment to Form PCT/ISA/210, Part VI
Continuation of OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

Group XII: Claims 22 and 24, drawn to a tenth product, vaccines using at least 5 amino acids of the env protein of MN-ST1.

Group XIII: Claim 23, drawn to an eleventh product, vaccines using at least 5 amino acids of the env protein of BA-L.

Group XIV: Claim 26, drawn to a twelfth product, a method of screening for drugs affecting HIV-1 activity.

Group XV: Claim 27, drawn to a thirteenth product, a bioassay to detect HIV-1 in biological samples.

The claims of Group I are drawn to a first product and a first specific method of use of the first product. Groups II-XV are drawn to separate products and methods of use of the products. PCT Rules 13.1 and 13.2 do not provide for multiple products and methods within a single general inventive concept. Note also 37 CFR § 1.475.

III DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	Cell, Vol. 40, issued January 1985, S. Wain-Hobson et al, "Nucleotide Sequence of the AIDS Virus, LAV," pages 9-17. See entire article.	1-24, 27
Y	Science, Vol. 227, issued 01 February 1985, R. Sanchez-Pescador et al, "Nucleotide Sequence and Expression of an AIDS-Associated Retrovirus (ARV-2)," pages 484-492. See entire article.	1-24, 27
Y	Nature, Vol. 313, issued 07 February 1985, M. A. Muesing et al, "Nucleic acid structure and expression of the human AIDS/lymphadenopathy retrovirus," pages 450-458. See entire article.	1-24, 27
Y	Nature, Vol. 320, issued 10 April 1986, S.-L. Hu et al, "Expression of AIDS virus envelope gene in recombinant vaccinia viruses," pages 537-540. See entire article.	2-24, 27
Y	Nature, Vol. 320, issued 10 April 1986, S. Chakrabarti et al, "Expression of the HTLV-III envelope gene by a recombinant vaccinia virus," pages 535-537. See entire article.	2-24, 27
Y	Bio/Technology, Vol. 3, issued October 1985, T. W. Chang et al, "Detection of Antibodies to Human T-Cell Lymphotropic Virus-III (HTLV-III) with an Immunoassay Employing a Recombinant Escherichia coli-Derived Viral Antigenic Peptide," pages 905-909. See entire article.	2-24, 27
Y	Proc. Natl. Acad. Sci. USA, Vol. 84, issued October 1987, J. R. Rusche et al, "Humoral immune response to the entire human immunodeficiency virus envelope glycoprotein made in insect cells," pages 6924-6928. See entire article.	2-24, 27
Y	J. Virology, Vol. 63, No. 3, issued March 1989, M. Hadzopoulou-Cladaras et al, "The rev (trs/art) Protein of Human Immunodeficiency Virus Type 1 Affects Viral mRNA and Protein Expression via a cis-Acting Sequence in the env Region," pages 1265-1274. See entire article.	2, 7, 9, 12, 14, 15, 16, 20, 21

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
Y	J. Virology, Vol. 64, No. 9, issued September 1990, P. J. Dillon et al, "Function of the Human Immunodeficiency Virus Types 1 and 2 Rev Proteins Is Dependent on Their Ability To Interact with a Structured Region Present in env Gene mRNA," pages 4428-4437. See entire article.	2, 7, 9, 12, 14, 15, 16, 20, 21
Y	Cell, Vol. 45, issued 06 June 1986, B. R. Starcich et al, "Identification and Characterization of Conserved and Variable Regions in the Envelope Gene of HTLV-III/LAV, the Retrovirus of AIDS," pages 637-648. See entire article.	2-24, 27
Y	J. Virology, Vol. 61, No. 2, issued February 1987, S. Modrow et al, "Computer-Assisted Analysis of Envelope Protein Sequences of Seven Human Immunodeficiency Virus Isolates: Prediction of Antigenic Epitopes in Conserved and Variable Regions," pages 570-578. See entire article.	2-24, 27
Y	Analytical Biochemistry, Vol. 151, issued 1985, D. Pauletti et al, "Application of a Modified Computer Algorithm in Determining Potential Antigenic Determinants Associated with the AIDS Virus Glycoprotein," pages 540-546. See entire article.	2-24, 27
Y	Virology, Vol. 164, issued 1988, C. Gurgo et al, "Envelope Sequences of Two New United States HIV-1 Isolates," pages 531-536. See entire article.	2-24, 27
Y	J. Virology, Vol. 64, No. 5, issued May 1990, A. Aldovini et al, "Mutations of RNA and Protein Sequences Involved in Human Immunodeficiency Virus Type 1 Packaging Result in Production of Noninfectious Virus," pages 1920-1926. See entire article.	19

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